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Rockville, MD

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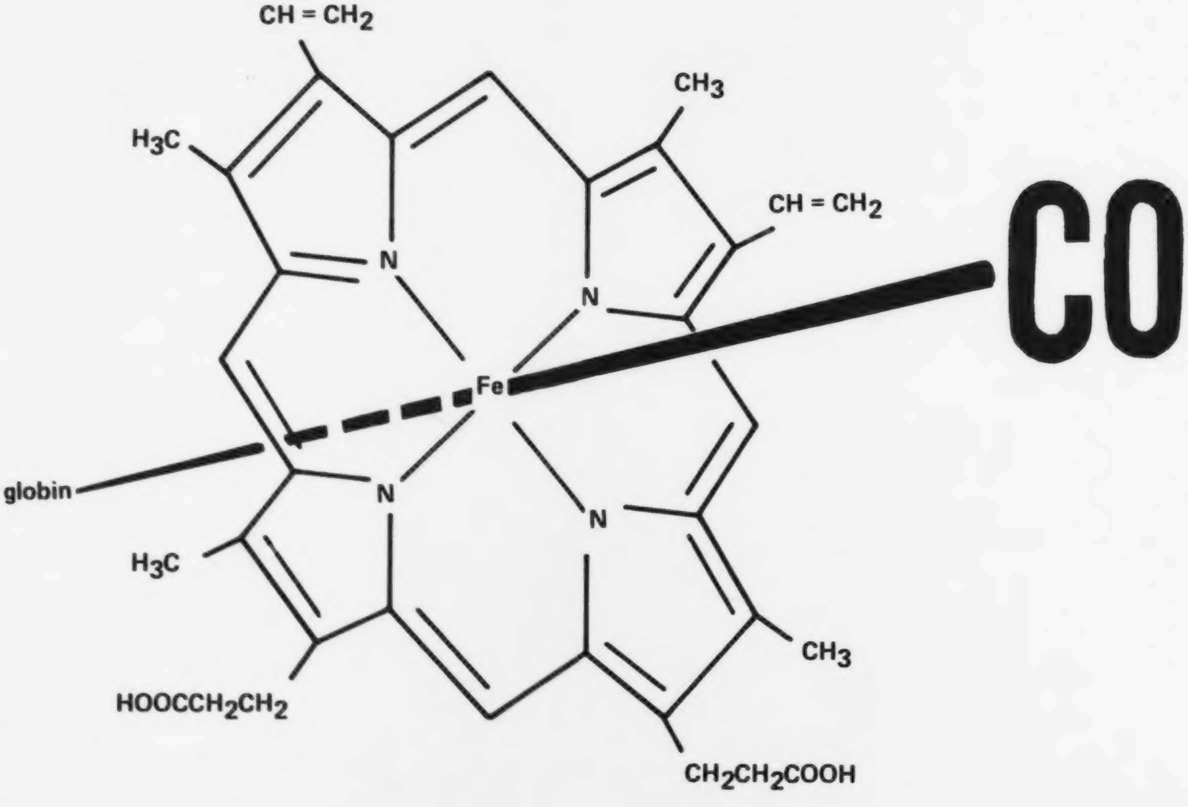
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Air Quality Criteria for Carbon Monoxide

U.S. ENVIRONMENTAL PROTECTION AGENCY
Environmental Criteria and Assessment Office
Office of Research and Development
Research Triangle Park, NC 27711

FOREWORD

This document has been prepared pursuant to Section 108(c) of the Clean Air Act, as amended, which requires that the Administrator from time to time review and, as appropriate, modify and reissue criteria issued pursuant to Section 108(a). Air quality criteria are required by Section 108(a) to reflect accurately the latest scientific information useful in indicating the kind and extent of all identifiable effects on public health and welfare that may be expected from the presence, in varying quantities, of a pollutant in the ambient air.

The original criteria document for carbon monoxide was issued in 1970. Since that time new information has been developed, and this document represents the modification and reissuance of the air quality criteria for carbon monoxide.

The regulatory purpose of these criteria is to serve as the basis for national ambient air quality standards promulgated by the Administrator under Section 109 of the Clean Air Act, as amended. Accordingly, as provided by Section 109(d), the Administrator has reviewed the national ambient air quality standards for carbon monoxide based on these revised criteria and is proposing appropriate action with respect to those standards concurrently with the issuance of this document.

The Agency is pleased to acknowledge the efforts of all persons and groups who have contributed, as participating authors or reviewers, to this document. In the last analysis, however, the Environmental Protection Agency is responsible for its content.

DOUGLAS M. COSTLE
Administrator
U.S. Environmental Protection Agency

PREFACE

This document consolidates and assesses current knowledge regarding the sources of carbon monoxide emissions and the effects they produce on health, vegetation, and materials.

The studies and data cited constitute the best available basis for specific standards aimed at protecting human health and the environment from carbon monoxide (CO) in ambient air. Various natural processes such as forest fires, oxidation of atmospheric methane, and biological activities maintain a CO background concentration of about 0.05 mg/m^3 (0.044 ppm). Additional CO from urban and industrial sources increases global concentrations to approximately 0.2 mg/m^3 (0.18 ppm) in the northern hemisphere and approximately 0.06 mg/m^3 (0.05 ppm) in the southern hemisphere. Within heavily populated areas such as cities, much higher concentrations of CO are found as a result of the local combustion of fossil fuels.

Carbon monoxide is a normal constituent of plants, which both metabolize and produce CO. It has been shown that adverse effects of CO on plants and various microorganisms require relatively high levels, which are considerably greater than those required for adverse health effects in animals and humans.

In mammals, endogenous sources of CO from metabolic activities result in levels of blood carboxyhemoglobin (COHb) of about 0.5 percent. Inhalation of CO from the ambient air may increase COHb to toxic levels because of the greater affinity of hemoglobin for CO than for oxygen. Thus, a lowered oxygen concentration in blood and tissues is created. Reductions in the oxygen content of blood caused by 5 to 10 percent COHb may be critical for patients suffering from cardiovascular diseases or chronic obstructive lung disease.

Experimental animal studies have indicated deleterious effects of CO upon the central nervous and cardiovascular systems. Adverse behavioral and central nervous system effects have been demonstrated at levels of 12 to 20 percent COHb, while adverse cardiovascular effects have been demonstrated at levels as low as 4 to 7 percent COHb.

The exposure of humans to concentrations of CO as low as 17 to 21 mg/m^3 (15 to 18 ppm) for eight hours, resulting in 2.5 to 3.0 percent COHb, adversely affects cardiovascular systems. Carbon monoxide exposures of 29 to 34 mg/m^3 (25 to 30 ppm) for 8 hours, resulting in COHb levels of 4 to 6 percent, have been shown to affect the central nervous systems of humans.

ABSTRACT

This document is an evaluation and assessment of scientific information relative to determining the health and welfare effects associated with exposure to various concentrations of carbon monoxide in ambient air. The document is not intended as a complete, detailed literature review. It does not cite every published article relating to carbon monoxide and its effects in the environment. The literature through 1978 has been reviewed thoroughly for information relative to criteria. The major gaps in our current knowledge, relative to criteria, have been identified.

Though the emphasis is on the presentation of data on health and welfare effects, other scientific data are presented and evaluated in order to provide a better understanding of the pollutants in the environment. To this end, separate chapters concerning the properties and principles of formation, emissions, analytical methods of measurement, observed ambient concentrations, the global cycle, effects on vegetation and microorganisms, mammalian metabolism, effects on experimental animals, and effects on humans are included.

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16. ABSTRACT

This document summarizes current scientific information regarding carbon monoxide (CO) as a component of the ambient atmosphere and the effects of CO upon man and the environment. The observed effects, as presented herein, constitute the basis for the criteria upon which the U.S. Environmental Protection Agency (EPA) will review the National Ambient Air Quality Standard (NAAQS) for CO. In the CO criteria document the following questions have been addressed: At what level of CO in the ambient air do detectable adverse health effects occur? What are these adverse health effects? What are the major sources of CO? Are there synergistic effects from CO exposure in humans living at high altitudes? Are present monitoring methods adequate to determine human exposure to CO? What are the global effects of increased CO emission into the atmosphere? It is in response to these and related questions that this document has been prepared.

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ABBREVIATIONS AND SYMBOLS

Å	Angstrom
$(A\text{-}aD_{O_2})$	Alveolar-artery pressure difference in O_2
AEROS	Aerometric and Emissions Reporting System
A/F	Air to fuel ratio
Amthauer's I.S.T.	Amthauer's Intelligence Structure Test
AQCR	Air Quality Control Regions
Ar	Argon
ASHD	Arteriosclerotic heart disease
ATM	Atomic pressure at sea level = 760 torr
BCG	Ballistocardiogram
°C	Degrees Centigrade (Celsius)
CAMP	Continuous Air Monitoring Program
CBF	Cerebral blood flow; also coronary blood flow
CFFF	Critical flicker fusion frequency
CH_4	Methane
CHD	Coronary heart disease
cm	Centimeter
CNS	Central nervous system
CNV	Contingent negative variation
CO	Carbon monoxide
CO_2	Carbon dioxide
COHb	Carboxyhemoglobin
COMb	Carboxymyoglobin
CV	Coefficient of variation; standard deviation divided by the mean
DCM	Dichloromethane; Methylene chloride; CH_2Cl_2
dl	Deciliter
dm	Decimeter
ECG	Echocardiogram
EDTA	Ethylene-diaminetetraacetic acid, often used as the disodium salt.
EKG	Electrocardiogram
EPA	Environmental Protection Agency
°F	Degrees Fahrenheit
g	Gram
H_2	Molecular hydrogen
Hb	Hemoglobin
HC	Hydrocarbons
HCN	Hydrocyanic acid
He	Helium
hg	Hectogram (100 g)
Hg	Mercury
HgO	Mercuric oxide
hv	The product of Planck's constant times the frequency of radiated energy (v) = quantum of energy (E). The amount of energy contained in a unitary particle of light of frequency v.

H_2O	Water
I_2O_5	Iodine pentoxide
k	Chemical reaction rate constant
kg	Kilogram
kJ/mol	Kilojoules per mole
km	Kilometer
Kr	Krypton
l	Liter
LDH	Lactate dehydrogenase
M	Haldane constant (in relation to carboxyhemoglobin); or, in atmospheric chemistry, an inert molecule or particle that participates in a chemical reaction
m	Meter
Mb	Myoglobin
MetHb	Methemoglobin
μg	Microgram
mg	Milligrams
ml	Milliliter
N_2	Molecular nitrogen
NAAQS	National Ambient Air Quality Standards
NADB	National Aerometric Data Bank
NBS	National Bureau of Standards
NDIR	Non-dispersive infrared photometry
nm	Nanometer
NO_2	Nitrogen dioxide
N_2O	Nitrous oxide; "laughing gas"
O_2	Molecular oxygen
O_3	Ozone
OH	Hydroxyl radical
O_2Hb	Oxyhemoglobin
P_{CO}	Partial pressure of carbon monoxide
P_{O_2}	Partial pressure of oxygen
ppb	Parts per billion
ppm	Parts per million
psi	Pounds per square inch
REM	Rapid eye movement
SAROAD	Storage and Retrieval of Aerometric Data
SF_6	Sulfur hexafluoride
SIP	State Implementation Plans
SRM	Standard Reference Materials
VER	Visual evoked response
VMT	Vehicle miles travelled
$\dot{V}_{O_2\,max}$	Maximal aerobic capacity
$(\dot{V}_A/\dot{Q})$	Ventilation perfusion ratio
2,3-DPG	2,3 - Diphosphoglycerate

1. SUMMARY AND CONCLUSIONS

INTRODUCTION

Section 109(d) of the Clean Air Act, as amended, requires a thorough review of the air quality criteria for carbon monoxide (CO) by December 31, 1980, and at five-year intervals thereafter. The Administrator of the Environmental Protection Agency (EPA) is required to make such revisions of the criteria as may be appropriate. In addition, the Administrator may from time to time review and, where appropriate, modify the criteria under the authority of Section 108(c).

This document is designed to evaluate the scientific information that will form the basis for the National Ambient Air Quality Standard (NAAQS) for CO. Major questions addressed in this document, which covers new research published since the original CO criteria document was issued, include the following:

(1) At what level of CO exposure do adverse health effects occur?

(2) What are the major health effects from exposure to CO?

(3) What are the special groups at risk to CO exposure?

(4) What are the major sources of CO exposure?

(5) Are there additive effects from CO exposure in combination with other pollutants and drugs, or at high altitudes?

(6) Do present monitoring methods adequately reflect human exposure to CO?

(7) What are the global effects of increased emissions of CO to the atmosphere?

PROPERTIES AND PRINCIPLES OF FORMATION OF CARBON MONOXIDE

Natural processes such as forest fires, methane oxidation, and biological activity maintain a CO background concentration of about 0.05 mg/m^3 (0.044 ppm). Global atmospheric mixing of CO from urban and industrial sources creates levels of about 0.2 mg/m^3 (0.18 ppm) in the northern hemisphere and about 0.06 mg/m^3 (0.05 ppm) in the southern hemisphere. Much higher levels exist in cities as a result of local combustion of fossil fuels.

On the average, nearly 85 percent of the CO in urban atmospheres is due to mobile sources. Carbon monoxide emissions from internal combustion engines can be reduced by improving the efficiency of combustion by changing designs and operating conditions, or by using catalytic reactors in the exhaust gas stream to oxidize CO to carbon dioxide (CO_2). The measurement of CO in effluent gas is used to indicate the proper and efficient operation of any combustion process. The reactions of CO with oxygen (O_2), ozone (O_3), and nitrogen dioxide (NO_2) are relatively slow, but the rapid oxidation of CO by OH radicals is an important factor affecting its abundance in the atmosphere.

ESTIMATION OF CARBON MONOXIDE EMISSIONS FROM TECHNOLOGICAL SOURCES

Nationwide, the estimated annual emission of CO from man-made sources in the U.S. rose from 102 million metric tons in 1970 to 104 in 1972. CO emissions declined to 97 million metric tons in 1975 and increased to 103 million metric tons in 1977. As of 1977, highway vehicles contributed 75.2 percent of the total emissions, non-highway transportation 8.2 percent, and industrial processes 8.1 percent. Miscellaneous combustion (agricultural burning, forest fires, structural fires, etc.) accounted for 4.8 percent, solid waste combustion 2.5 percent, and heat and electric power generation 1.2 percent of the total CO emissions.

Future emissions will depend on trends in vehicle use, the effectiveness of pollution control devices on automobiles, and the efficiency of vehicle operation. Based on estimates of the growth rate of vehicle use and the increased control of pollution, total CO emissions from automobiles in the U.S. are expected to decline after 1979. However, this forecast depends on trends that may change as a result of increased fuel prices, traffic flow improvements, conversion to alternate fuels, and maintenance of pollution control equipment.

ANALYTICAL METHODS

The EPA-approved method for measuring CO levels in ambient air utilizes non-dispersive infrared photometry (NDIR). NDIR is based on the characteristic absorption of infrared radiation by CO. The NDIR continuous monitoring systems are sensitive over a wide range of concentrations and have short response times. Because the systems are adversely affected by vibration or shock, they are unsuitable for mobile use.

The operating range of NDIR systems is up to 50 ppm CO. Very low back-ground levels of atmospheric CO can be measured by highly sensitive instruments, such as a gas chromatograph fitted with a flame ionization detector. Relatively high levels, for example, in parking garages, can be measured by the catalytic oxidation of CO measured by an electrochemical or a temperature-rise sensor depending on need for accuracy of results.

Blood carboxyhemoglobin (COHb) levels, which are a good index of CO exposure, can be measured by several techniques. These include spectrophotometry, gas chromatography or NDIR. Exhaled air also reflects the CO content of the blood if the air sample is collected under special conditions.

CARBON MONOXIDE CONCENTRATIONS IN AMBIENT AIR

The selection of monitoring sites is critical for the accurate assessment of CO exposure. Site selection depends on whether the monitoring program is designed for microscale, mesoscale, or macroscale air pollution regimes. For instance, the microscale regime should include monitoring sites along urban roadways, which have high CO concentrations.

Since 1962, continuous Air Monitoring Program (CAMP) stations have been operated by the Federal government at downtown sites in some major cities. Current measurements of CO levels are reported quarterly to the EPA by local, state, and Federal agencies. California, with 59 sites, has been the major contributor to the national CO data base. Measurements of CO levels disclose that the NAAQS are often exceeded, especially near major streets in urban areas. In 1977, 211 out of 456 monitors showed at least one 8-hour NAAQS violation, but only 11 showed 1-hour NAAQS violations.

Concentrations of CO vary with time, season, and geographic location. These variations often follow predictable trends. In most cities, CO levels peak from 7:00 to 9:00 a.m., 4:00 to 7:00 p.m., and 10:00 p.m. to midnight. The first two peaks arise from automobile traffic coupled with meteorological conditions. The midnight peak can be primarily attributed to calm wind conditions, which result in a reduced dispersion of CO emissions. The highest CO levels tend to occur in the fall and winter.

The dispersion of CO emissions is affected by wind speed, wind direction, atmospheric stability, vertical mixing height, and ambient temperature. In addition, this dispersion is affected by topographic features such as mountains and buildings.

Mathematical models have been proposed to describe CO transport, dispersion, and chemical transformations in the atmosphere. These models can be used to predict air quality CO levels on the basis of the characteristics of the emission sources plus meteorologic and topographic factors.

The following scenarios may result from exposure to unusually high ambient levels of CO. (1) On a big city freeway where traffic has come to a halt, the ambient CO level may exceed 50 mg/m^3 (44 ppm). (2) Inside a closed automobile where cigarettes are being smoked, CO concentrations may exceed 100 mg/m^3 (87 ppm). (3) In enclosed, unventilated garages, CO levels in excess of 115 mg/m^3 (100 ppm) have been found. (4) In a heavily traveled vehicular tunnel, a 1-hour maximum of 250 mg/m^3 (218 ppm) CO was recorded. (5) And for certain occupational exposures, such as those encountered by fire fighters and some foundry workers and miners, high CO levels have been reported.

THE GLOBAL CYCLE OF CARBON MONOXIDE

Much of the current discussion about the global cycle of atmospheric CO centers on the relative importance of the role of anthropogenic activity in the formulation of the global CO budget. Prior to 1970, nearly all CO emissions were thought to originate from combustion processes. However, in the early 1970s speculation evolved that a significant natural source of CO existed from the oxidation of methane in the unpolluted troposphere. Early estimates of the source strength of CO from methane oxidation indicated that this source was approximately ten times greater than man's input of CO into the atmosphere. With the advent of more sophisticated models, a better understanding of the geographic distribution of CO, and the availability of new chemical kinetics data, calculations in the late 1970s have suggested that methane oxidation is not the dominant source of CO in the atmosphere. Evidently, man's activities are responsible for the presence of much, and possibly most, of the CO observed in the atmosphere, especially in the northern hemisphere. If, indeed, anthropogenic sources of CO have perturbed the natural distribution of this gas in the troposphere, it seems likely that the abundance, distribution, and global cycles of many other trace constituents in the atmosphere have also been altered. Some studies even imply that increased amounts of CO may have a significant indirect influence on the chemistry that maintains the stratospheric ozone layer.

EFFECTS OF CARBON MONOXIDE ON VEGETATION AND CERTAIN MICROORGANISMS

Carbon monoxide is a normal constituent of the plant environment. Plants can both metabolize and produce CO. This may explain the relatively high levels of CO necessary to produce detrimental effects on plants.

There are few studies from which thresholds for detrimental or other effects might be inferred, although defoliation or inhibition of leaf and flower formation are demonstrable at high CO (above 100 ppm) concentrations. These studies are of little value in determining effects at ambient CO levels since the concentrations used were 1000 or more times greater than the usual atmospheric concentrations.

Microorganisms show a wide range of responses to CO, including its autotrophic oxidation. Thus, any change in global atmospheric concentration of CO might be expected to result in a corresponding alteration of the population distribution of soil microbes. Soil microflora are capable of responding to changing environmental conditions and may be considered as a buffering system and an eventual sink for CO.

Comparatively low levels of CO in the soil inhibit nitrogen fixation by soil microbes. Concentrations of 113 mg/m^3 (98 ppm) have been shown to reduce nitrogen fixation, while 572 to 1145 mg/m^3 (500 to 1000 ppm) result in nearly complete inhibition. An estimated consumption rate of 5×10^{14} g/yr CO indicates that soil microorganisms are a major sink for CO.

In higher plants, high concentrations of CO can induce the formation of adventitious roots, as well as stimulate the growth of latent root primordia. Plants exposed to 11,450 mg/m^3 (10,000 ppm) CO exhibit growth abnormalities including epinasty and hyponasty in leaves, retarded stem elongation, smaller and/or deformed leaves, and premature abscission of leaves. In Cannabis sativa, concentrations of CO in the 1145 to 11,450 mg/m^3 (1000 to 10,000 ppm) range can induce female expression in genetically male plants. Many species of plants are capable of absorbing and metabolizing CO photosynthetically. Although it has been demonstrated that plants absorb CO, they function as net producers, emitting more CO than they absorb.

METABOLISM OF CARBON MONOXIDE IN MAMMALS

The primary sources of carbon monoxide in mammals are the inhalation of ambient air and from the normal catabolism of pyrrole rings. Endogenous sources of CO result in COHb levels of approximately 0.5 percent. Any increment above this level is assumed to have resulted from an exogenous source. Factors that control and determine the final level of COHb are the concentration of inspired CO, alveolar ventilation, red cell volume, barometric pressure, and the diffusive capability of the lungs.

The apparent toxicity of CO is related to the strength of the coordination bond it forms with the iron atom in protoheme ($C_{34}H_{32}FeN_4O_4$). Hemoglobin (Hb), a ferrous iron complex of a protoporphyrin combined with globin, is contained within the erythrocyte (red blood cell). One of its primary functions is to transport O_2 and CO_2. Hemoglobin combines readily with either O_2 (to form O_2Hb) or CO (to form COHb). The affinity of Hb for CO is about 240 times greater than its affinity for O_2. The presence of COHb in blood not only reduces the availability of O_2 to the body but also inhibits the dissociation of the remaining O_2. Carbon monoxide also combines reversibly with heme compounds in the body cells.

A number of conclusions may be derived from Chapter 9, which covers the metabolism of carbon monoxide in mammals. The reduction in O_2-carrying capacity of the blood is proportional to the amount of COHb present. However, the amount of available O_2 is still further reduced by the inhibitory influence of COHb on the dissociation of any O_2Hb still available. Carbon monoxide diffuses more rapidly through blood and pulmonary and placental tissues than would be predicted from comparative solubilities of O_2 and CO in water. The small reductions in O_2 content at 5 to 10 percent COHb may be quite critical for patients suffering from cardiovascular diseases or chronic obstructive lung disease. It has been suggested that the principal mechanism of CO toxicity is not hypoxemia, but rather a blocking on the cellular level of the energy flow through the cytochrome system. The administration of CO results in chemoreceptor stimulation. The stimulation response appears to be almost linear with the COHb concentration, at least above 8 percent COHb. Available evidence suggests the presence of a biphasic decline in arterial blood COHb (percent) levels. The distribution phase, which persists for the first 20 to 30 minutes, is followed by a slower linear decline (elimination phase). And, although no final conclusion has been reached regarding the effects of CO on oxidative transport, experimental evidence suggests that the cytochromes are affected during CO poisoning.

EFFECTS OF CARBON MONOXIDE ON EXPERIMENTAL ANIMALS

Animal studies provide information that may be relevant to human reactions under similar circumstances. Animal data may permit predictions to be made concerning sensitive human populations, such as those with CNS and cardiovascular defects.

Carbon monoxide exposures of 58 mg/m^3 (50 ppm; 4 to 7 percent COHb) have produced cardiovascular effects. The minimal concentration of CO that affects behavior and CNS appears to be 115 mg/m^3 (100 ppm; 12 to 20 percent COHb).

EFFECTS OF LOW-LEVEL CARBON MONOXIDE EXPOSURE ON HUMANS

As in the animal studies, human exposures to low levels of CO have also resulted in deleterious effects on the CNS and cardiovascular systems. While an 8-hour exposure to 17 to 21 mg/m^3 (15 to 18 ppm; 2.5 to 3 percent COHb) CO affected cardiovascular systems, concentrations of CO as low as 29 to 34 mg/m^3 (25 to 30 ppm; 4 to 6 percent COHb) affected behavior and the CNS. Additionally, visual sensitivity may be dose-related, and a CO exposure resulting in 5-6 percent COHb reduces the capacity of persons to perform maximal work.

Fetuses, persons with cardiovascular or central nervous system defects, sickle cell anemics, young children, older persons, persons living at high altitudes, and those taking drugs comprise groups at special risk to CO exposure. The current literature offers little information regarding the high risk groups; however, it is apparent that exposure for 8 hours to CO concentrations as low as 15 to 18 ppm may be detrimental to the health of persons suffering cardiac impairment.

2. INTRODUCTION

This document has been prepared pursuant to Sections 108(c) and 109(d)(1) of the Clean Air Act, as amended. Section 108(c) requires that the Administrator of the EPA from time to time review and, as appropriate, modify and reissue criteria published pursuant to Section 108(a). Section 109(d)(1) requires both that the Administrator complete a thorough review and, as may be appropriate, make revisions in the criteria by December 31, 1980, and at five-year intervals thereafter. Air quality criteria are required by Section 108(a) to identify the effects on public health and welfare caused by varying amounts of pollutants in the air. These criteria must be supported by the latest available accurate scientific information.

The original criteria document for carbon monoxide (CO), The National Air Pollution Control Administration publication No. AP-62, was issued in 1970. Since that time, new information has been published. This document summarizes the pertinent information that will be used in considering whether the present CO standards are adequate or whether revisions are advisable or required.

The purpose of these criteria is to identify air pollution effects and serve as the basis for National Ambient Air Quality Standards promulgated by the Administrator under Section 109 of the Clean Air Act, as amended. This document, therefore, is concerned with CO as a pollutant and presents the presently available criteria upon which regulatory decision-making will be based. Specifically, air quality criteria for CO as a pollutant are intended to reflect accurately the latest scientific knowledge that may be used in predicting the kind and extent of all identifiable effects on public health and welfare that are traceable to the presence of CO in the ambient air. There are many factors and interactions that must be considered in the development of such a criteria document.

This document does not cite extensively the literature on excessively high levels of CO, but focuses on this pollutant as it is found in ambient environments. The intent is to present an updated comprehensive review of the available scientific information on CO as an air pollutant.

The basic chemistry and sources of CO must be considered before an understanding of the air pollution effects can be developed. Furthermore, it is necessary to consider the appropriateness of analytical techniques and methods so that proper assessment of concentration and potential exposure patterns can be made. Therefore, this information precedes the detailed discussion of the effects of CO on certain plants and microorganisms.

Ambient and experimental levels of CO are expressed in milligrams per cubic meter (mg/m^3) followed by a parenthetical expression of parts per million (ppm). Because gas density varies with pressure and temperature, an accurate expression of concentrations requires cognizance of these parameters. The conversion factor, for example, at a constant standard pressure of

760 mm Hg, at $0^{o}C$, 1 mg/m^3 equals 0.800 ppm and 1 ppm equals 1.250 mg/m^3; at $25^{o}C$, 1 mg/m^3 equals 0.874 ppm and 1 ppm equals 1.145 mg/m^3.

There is some indication that the production of CO and its concomitant release into the atmosphere may have significant effects on some aspects of the global atmosphere. Some attention is directed toward this question, as it may eventually affect human health and welfare.

The last three chapters deal with the metabolism of CO by animals and, most importantly, the effects CO has on animals and man. Naturally, much of this document is focused on the health and welfare of humans. Carbon monoxide is a pollutant that has at least one specific reaction product, carboxyhemoglobin (COHb), in the human system, which appears to be directly related to exposure and detrimental effects. Other physiological responses and reactions have been postulated recently and these are expected to aid in the elucidation of CO toxicity. Much of the physiological information is related to the concentration of COHb in the blood resulting from exposure to ambient or experimental levels of CO.

In the preparation of this document, much use was made of previous EPA documentation efforts on the subject as well as the monograph prepared by the National Academy of Sciences which was published late in 1977.

3. PROPERTIES AND PRINCIPLES OF FORMATION OF CARBON MONOXIDE

Even far from human habitation, carbon monoxide (CO) occurs in air at an average background concentration of 0.05 mg/m^3, primarily as a result of natural processes such as forest fires and the oxidation of methane. Much higher concentrations occur in cities from technological sources such as automobiles and the production of heat and power. Carbon monoxide emissions are increased when the fuel is burned in an incomplete or inefficient way. The physical and chemical properties of CO suggest that its atmospheric removal occurs primarily by reaction of CO with hydroxyl (OH) radicals.

INTRODUCTION

Carbon monoxide was first discovered to be a minor constituent of the earth's atmosphere by Migeotte[21] in 1948. While taking measurements of the solar spectrum, he observed a strong absorption band in the infrared region at 4.7 μm, which he attributed to CO.[18] On the twin bases of the belief that the solar contribution to that band was negligible and his observation of a strong day-to-day variability in absorption, Migeotte concluded that an appreciable amount of CO was present in the terrestrial atmosphere of Columbus, Ohio. In the 1950s many more observations[2,10,19,22,33,37] of CO were made, with measured concentrations ranging from 0.08 to 100 ppm. On the basis of these and other measurements available in 1963, Junge[17] stated that CO appeared to be the most abundant trace gas, other than carbon dioxide, in the atmosphere. The studies of Shaw[37] indicated higher mixing ratios near the ground than in the upper atmosphere, implying a source in the biosphere, but Junge emphasized that knowledge of the sources and sinks of atmospheric CO was extremely poor. It was not until the late 1960s that concerted efforts were made to determine the various production and destruction mechanisms for CO in the atmosphere.

The remainder of this chapter focuses on the physical properties and formation principles of CO that contribute to its release into the atmosphere. In Chapter 4, a review of the various factors that determine the technological emission source strength is discussed; in Chapter 7, other source strength estimates as well as the global cycle of CO are described.

PHYSICAL PROPERTIES

Carbon monoxide is a tasteless, odorless, colorless diatomic molecule that exists as a gas in the earth's atmosphere. Radiation in the visible and near ultraviolet regions of the electromagnetic spectrum is not absorbed by CO, although the molecule does have weak absorption bands between 125 and 155 nm. It absorbs radiation in the infrared region corresponding to the vibrational excitation of its electronic ground state. Carbon monoxide has a low electric dipole moment (0.10 debye), short interatomic distance (1.23 Å), and a high heat of formation from atoms, or bond strength (2072 kJ/mol). These observations suggest that the molecule is a resonance hybrid of three structures,[31] all of which contribute nearly equally to the normal ground state. General physical properties of CO are given in Table 3-1.

TABLE 3-1. PHYSICAL PROPERTIES OF CARBON MONOXIDE[24]

Molecular weight	28.01
Critical point	-140°C at 34.5 atm
Melting point	-199°C
Boiling point	-191.5°C
Density	
at 0°C, 1 atm	1.250 g/l
at 25°C,1 atm	1.145 g/l
Specific gravity relative to air	0.967
Solubility in water[a]	
at 0°C	3.54 ml/100 ml (44.3 ppmm)[b]
at 20°C	2.32 ml/100 ml (29.0 ppmm)
at 25°C	2.14 ml/100 ml (26.8 ppmm)
Explosive limits in air	12.5-74.2%
Fundamental vibration transition	2143.3 cm^{-1}
$CO(X'\Sigma_g^+, v' = 1\ Ev''0)$	(4.67 μm)
Conversion factors	
at 0°C, 1 atm	1 mg/m^3 = 0.800 ppm[c] 1 ppm = 1.250 mg/m^3
at 25°C, 1 atm	1 mg/m^3 = 0.873 ppm 1 ppm = 1.145 mg/m^3

[a] Volume of carbon monoxide is at 0°C, 1 atm (atmospheric pressure at sea level = 760 torr).

[b] Parts per million by mass (ppmm = mg/Kg).

[c] Parts per million by volume (ppm = mg/l).

GASEOUS CHEMICAL REACTIONS OF CARBON MONOXIDE

In its review of the gaseous chemical reactions of CO in 1970,[43] the National Air Pollution Control Administration (later to become part of the U.S. Environmental Protection Agency) concluded that no gaseous reactions have been shown to be important scavengers of CO in the atmosphere. No data since that time indicate that the processes they considered, which included reactions of CO with O_2, H_2O, NO_2, and O_3, are of any importance to atmospheric chemistry. However, the report did speculate that CO reactions with radicals in the atmosphere could provide an important sink for CO. Subsequent research has shown that the most important CO reaction in the atmosphere is OH radical attack. Other radicals react with CO much more slowly:[15]

$CO + HO_2 \rightarrow CO_2 + OH$, $k = 10^{-19}$ cm^3/(molecule x sec),

and $CO + CH_3O \rightarrow$ products, $k = 4 \times 10^{-17}$ cm^3/(molecule x sec).

Carbon monoxide also reacts with ground state,[39] and metastable,[4] atomic oxygen. The relative importance of these reactions to the overall chemistry occurring in the atmosphere is very slight. In the troposphere and stratosphere, $O(^3P)$ is much more likely to react with molecular oxygen, O_2, in a three-body reaction to form ozone, or with nitrogen dioxide, NO_2, to produce NO and O_2. Since $O(^1D)$ is a highly reactive species, it is more likely to react with water vapor, methane, or any other molecule that is more abundant than CO in the atmosphere. Collision of $O(^1D)$ with N_2 or O_2 is quite likely to bring this excited atom down to ground state. Thus, with the exception of the OH reaction, there is no evidence that any reactions involving CO are of any consequence in the atmosphere.

Many studies of the measurement of the reaction rate governing the reaction

$$CO + OH \rightarrow CO_2 + H$$

have appeared in the literature since the late 1960s (see Table 3-2). Until 1976, all of the measurements agreed fairly well, ranging between 1.3×10^{-13} cm^3/(molecule x sec) and 1.9×10^{-13} cm^3/(molecule x sec). The National Bureau of Standards review[15] recommended a value of 1.4×10^{-13} cm^3/(molecule x sec) and did not find any reason to believe that either a substantial temperature or pressure dependence existed for this reaction.

However, Cox et al.[6] reported a rate constant of 2.7×10^{-13} cm^3/ (molecule x sec) for this reaction at 760 torr (1 atm) using a mixture of N_2 and O_2 as the diluent gas. Sie et al.[38] likewise showed that the CO + OH reaction rate increased as the pressure in their reaction chamber increased when they used molecular hydrogen as a carrier gas. They also noted that the type of diluent employed for their experiments had an effect on the rate of reaction. Subsequent research efforts have supported the findings of Sie et al.[38] In general, it appears that there is no pressure effect if noble gases (for example, helium or argon) are used as the carrier gas, but when other gases, which may be more representative of the real atmosphere, are utilized in these studies the CO + OH reaction rate exhibits an important pressure dependence. Table 3-2 summarizes most of the reported studies of the CO + OH reaction. Most noteworthy about the recent efforts is the suggestion that the rate of

TABLE 3-2. REPORTED ROOM TEMPERATURE RATE CONSTANTS FOR THE REACTION OF OH RADICALS WITH CO

Rate constant (10^{-13} cm^3/molecule x sec)	Pressure, torr/ diluent gas	Reference
No observed pressure dependence		
1.91 ± 0.08	~ 1 (He or Ar)	Dixon-Lewis et al.
1.48 ± 0.15	100 (Ar)	Greiner
1.49 ± 0.05	not reported	Wilson and O'Donovan[46]
1.42	100 (He)	Greiner
1.66 ± 0.50	0.2--1.0 (Ar or He)	Mulcahy and Smith
1.35 ± 0.20	20 (He)	Stuhl and Niki[41]
1.33	1--3 (He or Ar)	Westenberg and deHaas[45]
1.44	10--20 (He or $N_2O + H_2$)	Smith and Zellner[39]
1.56 ± 0.2	0.3--6 (He, Ar or N_2)	Howard and Evenson
1.59	20 (He)	Davis et al.
1.58	20 (N_2)	Davis et al.
1.51 ± 0.08	730 (mostly Ar)	Gordon and Mulac
1.54 ± 0.16	25--654 (Ar)	Atkinson et al.
Pressure dependence observed		
1.00 ± 0.14	19.9 (H_2)	Sie et al.[37]
1.47 ± 0.19	83.4 (H_2)	
2.98 ± 0.19	296 (H_2)	
3.45 ± 0.22	702 (H_2)	
3.18 ± 0.29	774 (754 H_2 + 20 H_2O)	
1.19	627 (He)	
2.29	569 (SF_6)	
3.41	627 (SF_6)	
1.37 ± 0.20	100 (air)	Chan et al.
2.97 ± 0.16	700 (air)	
2.04	59 (He)	Overand and Paraskevopoulos[28]
3.24	200--359 (SF_6)	
1.50 ± 0.15	25 (Ar)	Perry et al.[31]
1.52 ± 0.15	75 (Ar)	
1.52 ± 0.16	225 (Ar)	
1.62 ± 0.19	406 (Ar)	
1.62 ± 0.24	643 (Ar)	
1.53 ± 0.16	25 (SF_6)	Perry et al.[31]
1.93 ± 0.20	76 (SF_6)	
2.40 ± 0.24	208 (SF_6)	
3.09 ± 0.31	404 (SF_6)	
3.43 ± 0.35	604 (SF_6)	

reaction is at least twice as fast at pressures representative of lower tropospheric conditions as was previously indicated. This observation has led to important changes in our understanding of the global CO cycle as well as the budgets of several other trace gases. These points are discussed in more detail in Chapter 7.

PRINCIPLES OF FORMATION

In all cases, the burning of any carbonaceous fuel produces, among other lesser products, two primary products: carbon dioxide (CO_2) and CO. The production of CO_2 predominates when the air or oxygen supply is in excess of the stoichiometric needs for complete combustion. If burning occurs under fuel-rich conditions, with less air or oxygen than is needed, CO will be produced in abundance. Most of the CO and CO_2 formed in past years was simply emitted into the atmosphere.

In recent years, concerted efforts have been made to reduce concentrations of potentially harmful materials in ambient air. Today, the CO in urban air originates almost entirely from local combustion processes. The background concentration of CO contributes less than 0.23 mg/m^3 (0.20 ppm) to the ambient air concentration at any given urban location. As a result of natural processes such as forest fires, oxidation of methane, and biological activity, the background level of CO is estimated to be about 0.05 mg/m^3 (0.04 ppm).[35] Global atmospheric mixing of urban and industrial pollutants probably accounts for a measured CO background of about 0.20 mg/m^3 (0.18 ppm) in the northern hemisphere and about 0.06 mg/m^3 (0.05 ppm) in the southern hemisphere.[36] The global average appears to be about 0.12 mg/m^3 (0.10 ppm) and does not appear to have been increasing substantially in recent years.[34]

Considerable effort has been made to reduce emissions of CO and other pollutants to the atmosphere. Generally the approach has been technological: reduction of CO emissions to the atmosphere either by improving the efficiency of the combustion processes, thereby increasing the yield of CO_2 and decreasing the yield of CO; or by applying secondary catalytic combustion reactors to the waste gas stream to convert CO to CO_2.

The development and application of control technology to reduce emissions of CO from combustion processes have generally been successful and are continuing to receive deserved attention. However, the 1977 amendments to the Clean Air Act[5] postpone meeting the desired automobile emission control schedules, reflecting in part the apparent difficulty encountered by the automobile industry in developing and supplying the required control technology. Since the automobile engine is recognized to be the major source of CO in most urban areas, special attention is given to the control of automotive emissions.

Table 3-3 shows the automobile emission control schedules that have resulted from the 1970 Clean Air Act and later amendments.

Table 3-3. AUTOMOBILE EMISSION CONTROL SCHEDULES[7] (g/mi)

	1976	1977	1978	1979	1980	1981	1982
1970 Clean Air Act							
HC	1.5	0.41	--	--	--	--	→
CO	15.0	3.4	--	--	--	--	→
NO_x	3.1	2.0	0.4	--	--	--	→
As of July 1, 1977							
HC	1.5		→0.41	--	--	--	→
CO	15		→3.4	--	--	--	→
NO_x	3.1	2.0	0.4				
1977 Amendments							
HC	1.5	--	--	--	→0.41		
CO	15	--	--		→7.0	3.4	→
NO_x	3.1	2.0				1.0	→

The problems encountered in mass producing and marketing effective control technology for automobile engines are complex, since a number of simultaneous requirements are involved, i.e., control of multiple air pollutants, fuel economy and efficiency, durability and quality control of components, and maintenance. Current testing[45] of automobiles having fuel injection and catalytic emission control systems has indicated that durability of the controls will be a problem in meeting the 1981 requirement of ≤3.4 g of CO per mile after 50,000 miles. (Emissions will be less than 3.4 g of CO per mile on new automobiles.)

The following subsections present a brief discussion of the general principles and mechanisms of CO formation and control of emissions associated with the many combustion processes. The processes are commonly classified in two broad types, mobile sources and stationary sources, since this division does generally separate distinct types of major combustion devices. Control techniques for CO emissions from mobile and stationary sources are detailed in references 27 and 28.

General Combustion Processes

Incomplete combustion of carbon or carbon-containing compounds creates varying amounts of CO. The chemical and physical processes that occur during combustion are complex, because they depend not only on the type of carbon compound reacting with oxygen, but also on the conditions existing in the combustion chamber.[20,30] Despite the complexity of the combustion process, certain general principles regarding the formation of CO from the combustion of hydrocarbon fuels are widely accepted.

Gaseous or liquid hydrocarbon fuel reacts with molecular oxygen in a chain of reactions that result in CO. Carbon monoxide then reacts with hydroxyl radicals to form carbon dioxide (CO_2). This second reaction is approximately ten times slower than the first. In coal combustion, too, the reaction of carbon and oxygen to form CO is one of the primary reactions, and a large fraction of carbon atoms go through the monoxide form. Again, the reaction of monoxide to dioxide is much slower.

Four basic variables control the concentration of CO in all combustion of hydrocarbon gases. These are: (1) oxygen concentration, (2) flame temperature, (3) gas residence time at high temperatures, and (4) combustion chamber turbulence. Oxygen concentration affects the formation of both CO and CO_2 because oxygen is required in the initial reactions with the fuel molecule and in the formation of the hydroxyl radical. As the availability of oxygen increases, more complete conversion of monoxide to dioxide results. Flame and gas temperatures affect both the formation of monoxide and the conversion of monoxide to dioxide because both reaction rates increase exponentially with increasing temperature. Also, the hydroxyl radical concentration in the combustion chamber is very temperature-dependent. The conversion of CO to CO_2 is also enhanced by longer residence time, because this is a relatively slow reaction in comparison with CO formation. Increased gas turbulence in the combustion zones increases the actual reaction rates by increasing the mixing of the reactants and assisting the relatively slower gaseous diffusion process, thereby resulting in more complete combustion.

Combustion Engines

Mobile Combustion Engines--Most mobile sources of CO are internal combustion engines of two types: (1) carbureted, spark-ignition, gasoline-fueled, reciprocating engines; and (2) diesel-fueled reciprocating engines. The CO emitted from any given engine is the product of the following factors: (1) concentration of CO in the exhaust gases, (2) the flow rate of exhaust gases, and (3) the duration of operation.

Internal Combustion Engines (Gasoline-Fueled, Spark-Ignition Engines)--Exhaust concentrations of CO increase with lower (richer) air-to-fuel (A/F) ratios, and decrease with higher (leaner) A/F ratios, but remain relatively constant with ratios above the stoichiometric ratio of about 15 to 1.[14] The behavior of gasoline automobile engines before and after the installation of pollutant control devices differs considerably. Depending on the mode of driving, the average uncontrolled engine operates at A/F ratios ranging from about 11 to 1 to a point slightly above the stoichiometric ratio. During the idling mode, at low speeds with light load (such as low speed cruise), during the full-open throttle mode until speed picks up, and during deceleration, the A/F ratio is low in uncontrolled cars and CO emissions are high. At higher speed cruise and during moderate acceleration, the reverse is true. Cars with exhaust controls generally remain much closer to stoichiometric A/F ratios in all modes, and thus the CO emissions are kept lower. The relationship between CO concentrations in engine exhaust and A/F ratios is shown in Figure 3-1. The exhaust flow rate increases with increasing engine power output.

Correlations between total emissions of CO in grams per vehicle mile and average route speed show a decrease in emissions with increasing average speed.[38,41,43] During low speed

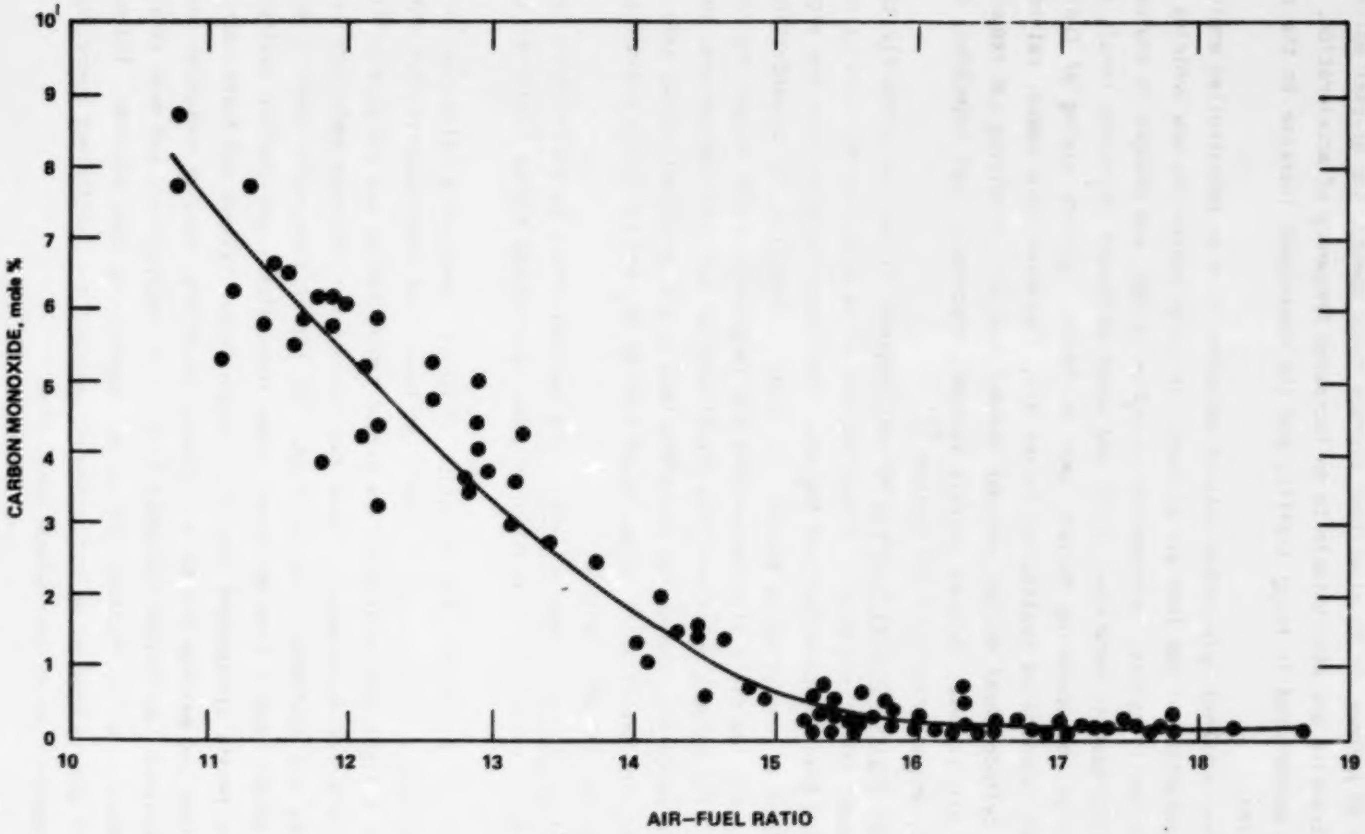

Figure 3-1. Effect of air-fuel ratio on exhaust gas carbon monoxide concentrations from three test engines.[14] (Used with permission of Society of Automotive Engineers, Inc. Copyright 1964.)

conditions (below 32 km/hour or 20 miles/hour average route speed), the greater emissions per unit of distance traveled are attributable to an increased frequency of acceleration, deceleration, and idling encountered in heavy traffic; and the consequent increase in the operating time per mile driven.

The CO and the unburned hydrocarbon exhaust emissions from an uncontrolled engine result from incomplete combustion of the fuel-air mixture. Emission control on new vehicles is being achieved by engine modifications, improvements in engine design, and changes in engine operating conditions. Substantial reductions in CO and other pollutant emissions result from consideration of design and operating factors such as leaner, uniform mixing of fuel and air during carburetion, controlled heating of intake air, increased idle speed, retarded spark timing, improved cylinder head design, exhaust thermal reactors, oxidizing and reducing catalysts, secondary air systems, exhaust recycle systems, electronic fuel injection, A/F ratio feedback controls, and modified ignition systems.[25]

Internal Combustion Engines (Diesel Engines)--Diesel engines in use are primarily the heavy-duty type that power trucks and buses. Diesel engines allow more complete combustion and use less volatile fuels than do spark-ignition engines. The operating principles are significantly different from those of the gasoline engine. In diesel combustion, CO concentrations in the exhaust are relatively low since high temperature and large excesses of oxygen are involved in normal operation. The exhaust emissions from diesel engines have the same general composition as gasoline engine emissions, though the concentrations of different pollutants vary considerably. For example, the diesel emits larger quantities of NO_x and polycylic organic particulates than gasoline engines; it emits less CO.

Stationary Combustion Sources (Steam Boilers)--This section refers to fuel-burning installations such as coal-, gas-, or oil-fired heating or power generating plants (external combustion boilers).

In these combustion systems, the formation of CO is lowest at a ratio near or slightly above the stoichiometric ratio of air to fuel. At lower than stoichiometric A/F ratios, high CO concentrations reflect the relatively low oxygen concentration and the possibility of poor reactant mixing from low turbulence. These two factors can increase emissions even though flame temperatures and residence time are high. At higher than stoichiometric A/F ratios, increased CO emissions result from decreased flame temperatures and shorter residence times. These two factors remain predominant even when oxygen concentrations and turbulence increase. Minimal CO emissions and maximum thermal efficiency, therefore, require combustor designs that provide high turbulence, sufficient residence time, high temperatures, and near stoichiometric A/F ratios. Combustor design dictates the actual approach to that minimum. The measurement of CO in effluent gas is used as an indication of improper and inefficient operating practice for any given combustor, or of inefficient combustion.

NON-COMBUSTION INDUSTRIAL SOURCES

There are numerous industrial activities that result in the emission of CO at one or more stages of the process.[44] Manufacturing pig iron can produce as much as 700 to 1050 kg CO/metric ton of pig iron. Other methods of producing iron and steel can produce CO at a rate of 9 to 118.5 kg/metric ton. However, most of the CO generated is normally recovered and used as fuel. Conditions such as "slips" can cause instantaneous emissions of CO. Slips have been greatly reduced with modern equipment. Grey-iron foundries can produce 72.5 kg CO/metric ton of product, but an efficient afterburner can reduce the CO emission to 4.5 kg/metric ton.

Charcoal production results in CO emissions of 160 kg/metric ton with or without the installation of chemical recovery equipment. Emissions from carbon black manufacture can range from 5 to 3200 kg CO/metric ton depending on the efficiency and quality of the emission control systems.

Some chemical processes such as phthalic anhydride production give off as little as 6 kg CO/metric ton with proper controls or as much as 200 kg CO/metric ton if no controls are installed. There are numerous other chemical processes that produce relatively small CO emissions per metric ton of product, such as sulfate pulping for paper at 1 to 30 kg CO/metric ton; lime manufacturing normally runs 1 to 4 kg CO/metric ton; and CO from adipic acid production is zero or slight with proper controls. Other industrial chemical processes that cause CO emissions are the manufacture of terephthalic acid and the synthesis of methanol and higher alcohols. As a rule, most industries find it economically desirable to install suitable controls to reduce CO emissions.

Even though some of these CO emission rates seem excessively high, they are, in fact, only a small part of the total pollutant load. Mention of these industries is made to emphasize the concern for localized pollution problems when accidents occur or proper controls are not used.

While the estimated CO emission resulting from forest wildfires in the United States for 1971 was 4×10^6 metric tons, the estimated total industrial process CO emission of the U.S. for 1971 was 10.3×10^6 metric tons.

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4. ESTIMATION OF CARBON MONOXIDE EMISSIONS FROM TECHNOLOGICAL SOURCES

The estimated total annual emissions from all man-made sources in the U.S. rose from 102 million metric tons in 1970 to 104 in 1972, then declined to 97 in 1975 and subsequently increased to 103 million metric tons in 1977. About 75 percent of the emissions total comes from highway vehicles, 8.5 percent from railroads, aircraft, and other non-highway transportation, 8 percent from industrial processes, 5 percent from miscellaneous combustion (forest fires, agricultural burning, structural fires, etc.), 2.5 percent from solid waste combustion, and 1 percent from combustion for heating and electric power generation.[8]

Total emission trends and emission rates for specific sources or source groups derived from calculated emission estimates provide a basis for assessing the magnitude and pattern of air pollution and allow the development of methods of estimating future air quality conditions.

The magnitude of future CO emissions will depend primarily upon vehicle use trends, the effectiveness of pollution control devices on automobiles, and the efficiency of vehicle operation. The concentrations of CO will generally be highest along congested major highways, because of vehicle exhausts. The interplay between the normal growth rate of vehicle use and the near-term increase in effectiveness of pollution control devices will probably cause total CO emissions from highway vehicles to decline after 1979.

NATIONAL EMISSION LEVELS

Estimates of the annual emissions of CO and other major air pollutants from all sources in the U.S. are summarized in Table 4-1 for the years 1970 through 1977.[8] It may be noted that 102.2 million metric tons of CO were discharged to the atmosphere in 1970. An increase is shown for 1971 and 1972 to 103.8 million metric tons and a subsequent decrease is shown for 1973, 1974, and 1975 to 96.9 million metric tons. In 1976 the emissions of CO rose to 102.9 million metric tons; in 1977 the figure was 102.7 million metric tons.

In Table 4-2,[8] total nationwide emissions are shown according to the source categories. The percentage contributed to the total national emission of CO by each of the designated source categories is shown in the last column.

The calculated nationwide annual emissions of CO from various source categories are compared for the years 1970 through 1977 in Table 4-3.[8] The estimations cited in Tables 4-1, 4-2, and 4-3 are the result of current methodology and refined emission factors and should not be compared with data reported earlier. These data show that from 1970 through 1977 the CO emissions increased by 0.5 percent. Since these data are only calculated estimates of total nationwide emissions, trends in emissions for local areas may be much different. Nevertheless, national emission estimates should be indicative of the general trend in the quantities of air pollutants released to the atmosphere.

TABLE 4-1. SUMMARY OF NATIONAL EMISSION ESTIMATES, 1970 to 1977[8]
(10^6 metric tons/yr)

Year	TSP[a]	SO_x	NO_x	VOC	CO
1970	22.2	29.8	19.6	29.5	102.2
1971	20.9	28.3	20.2	29.1	102.5
1972	19.6	29.6	21.6	29.6	103.8
1973	19.2	30.2	22.3	29.7	103.5
1974	17.0	28.4	21.7	28.6	99.7
1975	13.7	26.1	21.0	26.9	96.9
1976	13.2	27.2	22.8	28.7	102.9
1977	12.4	27.4	23.1	28.3	102.7

[a]TSP = total suspended particulates
SO_x = sulfur oxides
NO_x = nitrogen oxides
VOC = volatile organic compounds
CO = carbon monoxide

TABLE 4-2. NATIONWIDE EMISSION ESTIMATES, 1977[8]
(10^6 metric tons/yr)

Source category	TSP	SO_x	NO_x	VOC	CO	Percentage of total CO
Transportation	1.1	0.8	9.1	11.5	85.7	83.4
Highway vehicles	0.8	0.4	6.7	9.9	77.2	75.2
Non-highway vehicles	0.3	0.4	2.5	1.6	8.5	8.2
Stationary fuel combustion	4.8	22.4	13.0	1.5	1.2	1.2
Electric utilities	3.4	17.6	7.1	0.1	0.3	0.3
Industrial	1.2	3.2	5.0	1.3	0.6	0.6
Residential, commercial, and institutional	0.2	1.6	0.9	0.1	0.3	0.3
Industrial processes	5.4	4.2	0.7	10.1	8.3	8.1
Chemicals	0.2	0.2	0.2	2.7	2.8	2.7
Petroleum refining	0.1	0.8	0.4	1.1	2.4	2.3
Metals	1.3	2.4	0	0.1	2.0	2.0
Mineral products	2.7	0.6	0.1	0.1	0	0
Oil & marketing & gas production	0	0.1	0	3.1	0	0
Industrial organic solvent use	0	0	0	2.7	0	0
Other processes	1.1	0.1	0	0.3	1.1	1.1
Solid waste	0.4	0	0.1	0.7	2.6	2.5
Miscellaneous	0.7	0	0.1	4.5	4.9	4.8
Forest wildfires	0.5	0	0.1	0.7	4.3	4.2
Agricultural burning	0.1	0	0	0.1	0.5	0.5
Coal refuse burning	0	0	0	0	0	0
Structural fires	0.1	0	0	0	0.1	0.1
Miscellaneous organic solvent use	0	0	0	3.7	0	0
Total	12.4	27.4	23.1	28.3	102.7	100 100

Note: A zero indicates emissions of less than 50,000 metric tons.

TABLE 4-3. NATIONWIDE CARBON MONOXIDE EMISSION ESTIMATES, 1970 to 1977[8]
(10^6 metric tons/yr)

Source category	1970	1971	1972	1973	1974	1975	1976	1977
Transportation	80.5	81.1	85.4	85.9	81.7	82.0	85.1	85.7
Highway vehicles	70.9	71.7	76.1	76.5	73.3	73.8	75.6	77.2
Non-highway vehicles	9.6	9.4	9.3	9.4	8.4	8.2	8.5	8.5
Stationary fuel combustion	1.3	1.4	1.3	1.4	1.3	1.1	1.2	1.2
Electric utilities	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3
Industrial	0.6	0.6	0.6	0.6	0.6	0.5	0.6	0.6
Residential, commercial, and institutional	0.5	0.6	0.5	0.5	0.4	0.3	0.3	0.3
Industrial processes	8.0	7.9	7.9	8.2	8.2	7.3	7.8	8.3
Chemicals	2.9	2.7	2.5	2.7	2.5	2.2	2.4	2.8
Petroleum refining	2.1	2.1	2.2	2.2	2.3	2.4	2.4	2.4
Metals	1.1	2.2	2.3	2.3	2.4	1.8	1.9	2.0
Mineral products	0	0	0	0	0	0	0	0
Oil & gas production & marketing	0	0	0	0	0	0	0	0
Industrial organic solvent use	0	0	0	0	0	0	0	0
Other processes	0.9	0.9	1.0	1.0	1.0	0.9	1.1	1.1
Solid waste	6.2	4.7	4.0	3.6	3.2	2.9	2.9	2.6
Miscellaneous	6.2	7.4	5.2	4.4	5.3	3.6	5.9	4.9
Forest wildfires	4.3	5.9	4.2	3.5	4.5	3.0	5.3	4.3
Agricultural burning	1.5	1.2	0.8	0.7	0.6	0.5	0.5	0.5
Coal refuse burning	0.3	0.2	0.1	0.1	0.1	0	0	0
Structural fires	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Miscellaneous organic solvent use	0	0	0	0	0	0	0	0
Total	102.2	102.5	103.8	103.5	99.7	96.9	102.9	102.7

Note: A zero indicates emissions of less than 50,000 metric tons per year.

Overall, carbon monoxide emissions have not changed significantly during the period 1970 to 1977. Emissions have been reduced as a result of less burning of solid waste and agricultural materials. However, despite controls implemented on highway motor vehicles, total emissions from this source category have increased by about 9 percent,[8] owing to the increase in vehicle miles traveled.

EMISSIONS AND EMISSION FACTORS BY SOURCE TYPE

Mobile Combustion Sources

Table 4-3 shows the nationwide annual emission estimates for the "transportation" category, which includes emissions from all mobile sources. Highway vehicles include passenger cars, trucks, and buses. Non-highway vehicles include aircraft, railroads, vessels, and miscellaneous mobile engines such as farm equipment, industrial and construction machinery, lawnmowers, and snowmobiles. The estimated emissions of CO by highway vehicles in 1977 was 77.2 million metric tons and by non-highway vehicles, 8.5 million metric tons, representing 75.2 percent and 8.2 percent, respectively, of the total national emissions of CO.

For localized pollutants such as CO, the ability of test procedures to predict changes in emissions depends on the similarity of the localized driving pattern and associated operating conditions to those in the test procedure. The EPA, therefore, has developed a series of correction factors to expand upon the light duty vehicle (LDV) and heavy duty vehicle (HDV) test procedures in order to predict emissions from a large number of user-specific scenarios. Data required to develop these correction factors have been generated by means of carefully designed statistical studies that test consumer-owned vehicles. Composite average emission factors that have been determined for a number of combinations of operating conditions and vehicle mixes are available in the literature.[6,7]

The data collected in the EPA exhaust emission surveillance programs are analyzed to provide mean emissions by model-year vehicle in each calendar year, change in emissions with the accumulation of mileage, change in emissions with vehicle age, percentage of vehicles complying with standards, and effect on emissions of vehicle parameters (engine displacement, vehicle weight, etc.). These surveillance data, along with prototype vehicle test data, assembly line test data, and technical judgment, form the basis for existing and projected mobile source emission factors.[6,7]

Combustion for Power and Heat

Table 4-3 shows the nationwide annual emission estimates for the "stationary fuel combustion" category, which includes all stationary combustion equipment such as boilers and stationary internal combustion engines.

The specific emission factors for stationary fuel combustors vary according to the type and size of the installation and the fuel used, as well as the mode of operation. The EPA compilation of air pollutant emission factors[6] provides emission data obtained from source tests, material balance studies, engineering estimates, etc., for the various common emission categories.

Technological Processes Producing Carbon Monoxide

Table 4-3 shows the nationwide annual emission estimates for the "industrial processes" category, which includes the emissions resulting from the operation of process equipment by industries manufacturing chemicals, refining petroleum, producing metals and metal products, and by other processing industries (combining the emissions from pulp and paper, wood products, agricultural, rubber and plastics, and textile industries).

The specific emission factors for the various applicable processes used in these manufacturing industries are detailed in the EPA compilation of air pollution emission factors.[6] Some specific information on the CO emissions from industries is included in Chapter 3.

Solid Waste Combustion

Table 4-3 shows the nationwide annual emission estimates for the "solid waste" category, which includes the emissions resulting from the combustion of wastes in municipal and other incinerators, and from the open burning of domestic and municipal refuse.

Specific emission factors for the various waste combustion procedures in use are detailed in the EPA compilation of air pollution emission factors.[6]

Miscellaneous Combustion

Table 4-3 shows the nationwide annual emission estimates for a "miscellaneous" category, which includes emissions from combustion of forest, agricultural, and coal refuse materials and from structural fires.

Emission factors specific to the materials combusted and the methods used are detailed in the EPA compilation of air pollution emission factors.[6]

ESTIMATION OF FUTURE EMISSION LEVELS

Future exposure to ambient CO concentrations will clearly depend upon future amounts and patterns of CO emissions into the atmosphere. Since highest concentrations of CO generally result from auto emissions, substantial research effort has been expended to characterize those emissions accurately. Recently, the EPA[5] has administered a series of exhaust emission surveillance programs in order to characterize how well vehicles perform in actual use. Based on these surveillance data, the EPA[7] has published a method for calculating existing and projected mobile source emission factors and has tabulated average highway vehicle emission factors for 21 different combinations of operating conditions and vehicle mixes.

Table 4-4 presents the estimated vehicle emission factors in units of grams of CO per vehicle mile (and per vehicle kilometer) for the years 1970 through 1999 and for two selected highway scenarios. These data are plotted in Figure 4-1, which illustrates the projected decrease in CO emissions per vehicle kilometer of travel as a result of the gradual replacement of vehicles without emission control equipment by vehicles with control equipment. The rate of yearly decrease in CO emission factors (i.e., the slope of the curve) is also affected by the gradual deterioration of emission control equipment with accumulated age and mileage.

TABLE 4-4. AVERAGE VEHICLE EMISSION FACTORS FOR TWO SELECTED HIGHWAY SCENARIOS

	AVERAGE EMISSION FACTORS			
	Condition A		Condition B	
Year	G/mi	G/km	G/mi	G/km
1970	86.9	54.0	85.6	53.2
1971	83.9	52.1	82.4	51.2
1972	81.6	50.7	80.0	49.7
1973	80.0	49.7	78.2	48.6
1974	79.0	49.1	77.1	47.9
1975	77.0	47.8	75.1	46.6
1976	74.3	46.1	72.5	45.0
1977	71.4	44.3	69.9	43.4
1978	68.3	42.4	67.1	41.7
1979	65.2	40.5	64.3	39.9
1980	60.6	37.6	60.2	37.4
1981	55.5	34.5	55.8	34.7
1982	50.6	31.4	51.6	32.0
1983	45.7	28.4	47.2	29.3
1984	40.9	25.4	42.9	26.6
1985	36.7	22.8	38.9	24.2
1986	33.0	20.5	35.2	21.9
1987	30.0	18.6	32.2	20.0
1988	27.6	17.1	29.5	18.3
1989	25.6	15.9	27.3	17.0
1990	24.2	15.0	25.6	15.9
1991	23.1	14.3	24.1	15.0
1992	22.2	13.8	23.0	14.3
1993	21.5	13.4	22.1	13.7
1994	21.1	13.1	21.4	13.3
1995	20.7	12.9	20.8	12.9
1996	20.7	12.9	20.8	12.9
1997	20.7	12.9	20.8	12.9
1998	20.7	12.9	20.8	12.9
1999	20.7	12.9	20.8	12.9

Speed: 19.6 mph (31.6 kph); Temperature: 75°F, % cold start: 20.6% and % hot start: 27.3%.

Condition A: Vehicle miles traveled = 8.3% automobiles, 5.8% for each of the two light truck classes, 4.5% heavy gas trucks, 3.5% heavy duty diesels, and 0.5% motorcycles, approximating national vehicle miles traveled mix.

Condition B: Vehicle miles traveled = 63% automobiles, 16% for each of the two light truck classes, 2.5% heavy gas trucks, and 2.5% heavy duty diesel vehicles, approximating a mix of vehicle miles traveled that might be found in a central city area.

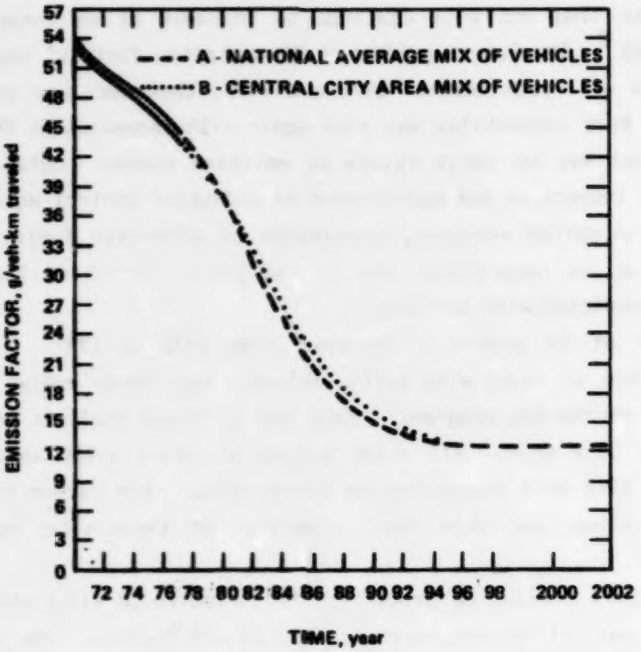

Figure 4-1. Average composite emission factors for carbon monoxide.[7]

Total CO emission rates are also reflected by vehicle-use trends. Over the past 20 years, there has been an average increase of 4.6 percent a year[1,3,4] in vehicle miles of travel. Vehicle miles of travel (VMT) increased 4.6 percent in 1971 and 1972, 2.4 percent in 1973 and 1974, 3.4 percent in 1975, and 5.9 percent in 1976. Federal Highway Administration projections indicate that VMT will continue to increase at an annual average rate of 2.2 percent through 1999.[2] The latest published EPA emission factors[7] suggest that CO emissions from mobile sources will peak between 1973 and 1979, then decrease until 1994. After 1994, total CO emissions from automobiles may rise again with increases in VMT. There are a number of other factors that may influence future CO emission trends: delay of the clean car performance standards, inspection and maintenance of pollution control equipment, possible retrofit of less well-controlled vehicles, conversion to alternate fuels, traffic flow improvements, motor vehicle use restraints, use of car pools, increased fuel prices, etc. These factors cannot be predicted with certainty.

Ambient levels of CO generally improved from 1972 to 1977. There was a 20 percent increase in the number of sites with sufficient data for trends analysis due to the expansion of state and local monitoring programs. Data for CO trend analysis were obtained from EPA's National Aerometric Data Bank. All sites having at least 4,000 annual values during both 1972-1974 and 1975-1977 were designated as trend sites. For carbon monoxide, 243 sites met this selection criterion, and more than 80 percent of these sites had at least 4 years of data.

During the 1972-77 period, 80 percent of the selected CO sites showed long-term improvement and this trend was fairly consistent for all 10 EPA Regions. The median rate of improvement for the 90th percentile of 8-hour values was approximately 6 percent per year. From 1976 to 1977, 70 percent of the 243 sites improved. Consistent with this downward trend, almost one third of these sites reported their lowest values in 1977.

In discussing the relationship between ambient CO levels and CO emissions, it is important to clarify certain components involved in estimating CO emissions. Two key factors are the vehicle miles traveled (VMT) and the emissions per VMT. In its simplest form, total CO emissions may be viewed as merely the product of emissions per mile multiplied by the number of miles traveled. Total CO emissions in 1976-77 were higher than in 1974-75. During this time, the emissions per VMT actually decreased due to emission controls, but this was more than offset by an even greater increase in VMT. The net effect was an overall increase in total CO emissions. Translating these emission components in terms of ambient CO levels, it would be reasonable to expect improvement at downtown locations that are saturated with traffic because the emissions per mile reductions would outweigh any increase in VMT. On the other hand, growth areas could record increases in ambient CO levels because increases in VMT offset the reduction in emissions per VMT.[8]

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5. ANALYTICAL METHODS FOR MEASUREMENT OF CARBON MONOXIDE

It is impossible to monitor and maintain air quality (or even to study the health effects of pollutants) without reliable methods for measuring the amount of pollutant present. This chapter surveys the analytical methods for measuring carbon monoxide (CO) in air and in blood and comments on some of the sampling techniques.

INTRODUCTION

To promote uniform enforcement of the air quality standards set forth under the Clean Air Act as amended,[33] the EPA has established provisions under which analytical methods can be designated as "reference" or "equivalent" methods.[175] A reference method or equivalent method for air quality measurements is required for acceptance of measurement data by EPA. An "equivalent method" can be so designated when an analytical method is shown to produce results equivalent to an approved NDIR method.

At present the reference methods for monitoring CO in the atmosphere must be based on non-dispersive infrared photometry (NDIR). In addition, before a particular NDIR instrument can be used in a reference method, it must be designated by the EPA as approved in terms of manufacturer, model number, components, operating range, etc. Several NDIR instruments have been so designated. No equivalent methods that use a principle other than NDIR have as of this writing been designated for measuring CO in ambient air.

An operating range of up to 58 mg/m^3 (0 to 50 ppm) CO in air is typical for the NDIR instruments designated for reference method use. Analytical capability is needed not only for this range but also for a narrower range up to 1 mg/m^3 (0 to 1 ppm) to measure background levels in unpolluted atmospheres and for a wider range up to 1150 mg/m^3 (up to 1000 ppm) to measure high concentrations, such as those in vehicular tunnels, smoke-filled rooms, and parking garages.

There is a recognized need to relate results obtained by other methods (including those used in health effects and field studies) to those obtained by the NDIR reference method, but this is difficult because reported information about other methods is inadequate as to variations in operator competence and effects of experimental conditions.

Overview of Techniques for Measurement of Carbon Monoxide in Air

In the past decade, there have been several excellent reviews on the measurement of CO in the atmosphere.[43,54,74,87,97,136,145,164,169,170,184] For monitoring, the best technique at present is non-dispersive infrared photometry,[49,81,111,112,125,128,148,149,157,158] usually with a Luft-type detector.[102] A more sensitive method, suitable for measuring background levels, is gas chromatography.[19,22,46,130,160,167,168] For high levels, a useful technique is catalytic oxidation of the CO, by Hopcalite or other catalysts,[163] either with temperature-rise sensors[117,129,145] or with electrochemical sensors.[12,13,19,50,136,144]

Other analytical schemes used for CO in air include: infrared gas-filter correlation, a refinement of NDIR;[1,11,24,25,65,68,69,75,187] dual isotope infrared fluorescence, another technique derived from NDIR;[101,107,108] reaction with hot mercuric oxide to give elemental mercury vapor;[14,110,115,123,138] reaction with heated iodine pentoxide to give elemental iodine;[2,113,118,179,186] and color reactions,[4,15,60,88,92,98,135,154,161] as with palladium salts or the silver salt of p-sulfamoylbenzoate. Many of these methods are described in the section on Measuring Carbon Monoxide in Air. A classical procedure for many decades was to use gasometric apparatus such as the Orsat or Haldane,[44] in which the CO present in a gas sample is absorbed by cuprous chloride solution, and the decrease in volume or pressure is measured. This method, however, is not sensitive enough for trace amounts.

Microwave rotational spectroscopy promises to be an analytical technique with high specificity.[82,114] Other possible ways to determine CO include: chemiluminescent reaction with ozone,[180] X-ray excited optical fluorescence,[66] radiorelease of ^{85}Kr from the kryptonates of mercuric oxide or iodine pentoxide,[67,116] and utilization of narrow-band infrared laser sources.[8,64]

Calibration Requirements

Whichever method or instrument is used, it is essential that the results be validated by frequent calibration with samples of known composition similar to the unknowns.[42,176,178] Chemical analyses can be relied on only after the analyst has achieved acceptable accuracy in the analysis of such standard samples through an audit program.

PREPARATION OF CARBON MONOXIDE GAS STANDARD REFERENCE MATERIALS

Gravimetric Method

A set of reliable gas standards for CO in air certified at levels of approximately 12, 23, and 46 mg/cm^3 (10, 20, and 40 ppm) is obtainable from the National Bureau of Standards (NBS), Washington, D.C.[178] These NBS Standard Reference Materials (SRMs) are supplied as compressed gas (at about 1700 psi) in high-strength aluminum cylinders containing 31 ft^3 of gas at dry standard temperature and pressure and are accurate to better than 1 percent of the stated values. Because of the time and effort required in their preparation, SRMs are not intended for use as daily working standards, but rather as primary standards against which transfer standards can be calibrated.

The gravimetric method used by NBS for preparing primary standards of CO[83,84] is as follows. An empty gas cylinder is tared on an analytical balance; then 2 g of pure CO, weighed accurately to ±2 mg, is added from a high-pressure tank. Next, 100 g of pure air (accurately weighed) is added from a pressure tank, and the concentration of CO is calculated from the sum of the respective weights added to the molecular weights of the two gases. Not only the average "molecular weight" of the air, but also the requisite careful check of purity, is obtained by mass spectrometry and gas chromatography analyses of the air and the CO. Lower-concentration primary standards are prepared by serial dilutions (not more than a factor of 100 for each step) by the same technique.

The commercial suppliers of compressed gases are another source of air samples containing CO in the mg/m^3 or ppm range. However, the nominal values for CO concentration supplied by the vendor should be verified by intercomparison with an SRM or other validated standard sample. A three-way intercomparison has been made among the NBS SRMs, commercial gas blends, and an extensive set of standard gas mixtures prepared by gravimetric blending at the Environmental Protection Agency.[124] Results of the comparison showed that commercial gas blends are within ±2 percent of the true value represented by a primary standard. Another study on commercial blends[59] found poorer accuracy. To achieve compatible results in sample analyses, different laboratories should interchange and compare their respective working standards frequently.

In making and using standards, many precautions are needed;[83] one deserves special mention. Large but unpredictable decreases in CO concentration occur within a few months in mixtures prepared in ordinary mild steel gas cylinders, as shown in Figure 5-1. This may be due to carbonyl formation or oxidation to carbon dioxide. The difficulty can be avoided by the use of gas cylinders made of stainless steel or aluminum. A special treatment for aluminum, which includes enhancement of the aluminum oxide surface layer, has been recommended.[188]

In addition to the set of Standard Reference Materials for CO in air, another set of SRMs is available from NBS for CO in nitrogen. This second set covers concentrations from 10 to 957 ppm.

Volumetric Gas Dilution Methods

Standard samples of CO in air can also be prepared by volumetric gas dilution techniques. In a versatile system designed for this purpose,[85] air at a pressure of 10 to 100 psi is first purified and dried by passage through cartridges of charcoal and silica gel, then passed through a sintered metal filter into a flow control and flowmeter system. The CO (or a mixture of CO in air that is to be diluted further), also under pressure, is passed through a similar flow control and flowmeter system.

Both gas streams are led into a mixing chamber, which is designed to mix the gas streams rapidly and completely before passage into the sampling manifold from which the standard samples will be withdrawn. From the air flow rate, F_A, and the CO flow rate, F_{co}, the concentration of CO in the sample, C_{co}, is readily calculated by the expression

$$C_{co} = \frac{F_{co}}{F_{co} + F_A} .$$

For samples prepared by dilution of a more concentrated bulk mixture, the concentration is given by

$$C_{co} = \frac{F_b}{F_b + F_A} (C_b),$$

where F_b and C_b are the values of flow rate and concentration of CO, respectively, for the bulk mixture.

Other Methods

Permeation tubes have been used for preparing standard mixtures of such pollutant gases as sulfur dioxide and nitrogen dioxide.[119,143] Although the tubes are not routinely used in

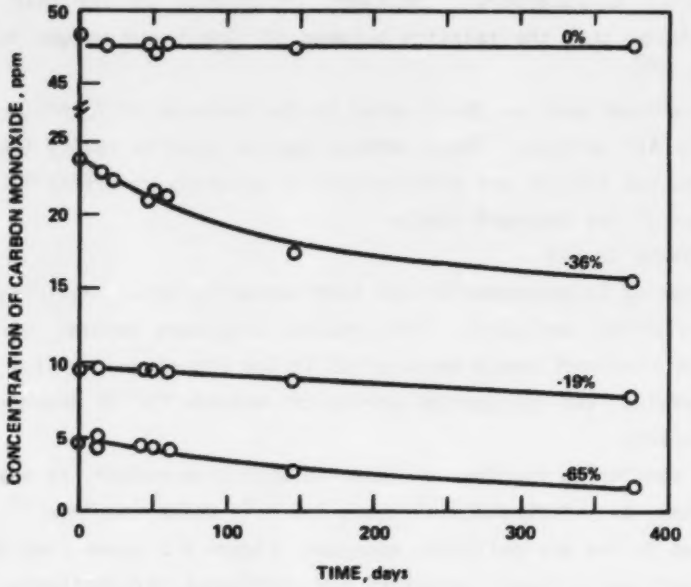


Figure 5-1. Loss of carbon monoxide with time in mild steel cylinders.[83]
(Used with permission of ISA Transactions, Vol. 14, No. 4 Copyright Instrument Society of America, 1975.)

the United States for making CO standard samples, they are believed to be in use in Europe. In the permeation tube technique, a sample of the pure gas under pressure is allowed to diffuse through a calibrated partition at a defined rate into a diluent gas stream, to give a standard sample of known composition.

Another possible way to liberate known amounts of CO into a diluent gas is by thermal decomposition of nickel tetracarbonyl. However, an attempt to use this as a gravimetric calibration source showed that the relation between CO output and weight loss of the $Ni(CO)_4$ is non-stoichiometric.[162]

Chemical assay methods such as those noted in the Overview of Techniques for Measurement of Carbon Monoxide in Air section. These methods can be used to verify the CO concentration in a standard mixture, but they do not provide greater accuracy or reliability than is attained by careful preparation of the standard sample.

MEASURING CARBON MONOXIDE IN AIR

Ambient CO monitoring is an expensive and time-consuming task, requiring skilled personnel and sophisticated analytical equipment. This section discusses several important aspects of the continuous and intermittent measurement of CO in the atmosphere, including sampling techniques, sampling schedules, and recommended analytical methods for CO measurement.

Sampling System Components

Carbon monoxide monitoring requires a sample introduction system, an analyzer system, and a data recording system, as illustrated in Figure 5-2.[174] While the "heart" of any air pollution monitoring system is the air pollution analyzer, Figure 5-2 shows that there is a considerable amount of supportive equipment necessary for continuous air monitoring.

A sample introduction system consists of a sampling probe, an intake manifold, tubing, and air movers. This system is needed to collect the air sample from the atmosphere and to transport it to the analyzer without altering the original concentration. It may also be used to introduce known gas concentrations in order to check periodically the reliability of analyzer output. Construction materials for the sampling probe, intake manifold, and tubing should be tested to demonstrate that the test atmosphere composition or concentration is not significantly altered. It is recommended that sample introduction systems be fabricated from borosilicate glass or FEP Teflon®[37] if all pollutants are to be monitored. However, in monitoring for CO only, it has been reported[191] that no measurable pollutant losses were observed when sampling systems were constructed of tygon, polypropylene, polyvinylchloride piping, aluminum, or stainless steel. The sample introduction system should be constructed so that it presents no pressure drop to the analyzer.

The analyzer system consists of the analyzer itself and any sample preconditioning components that may be necessary. Sample preconditioning might require a moisture control system to help minimize the false positive response of the analyzer (e.g., the NDIR analyzer) to water vapor, and a particulate filter to help protect the analyzer from clogging and possible chemical interference due to particulate buildup in the sample lines or analyzer inlet.

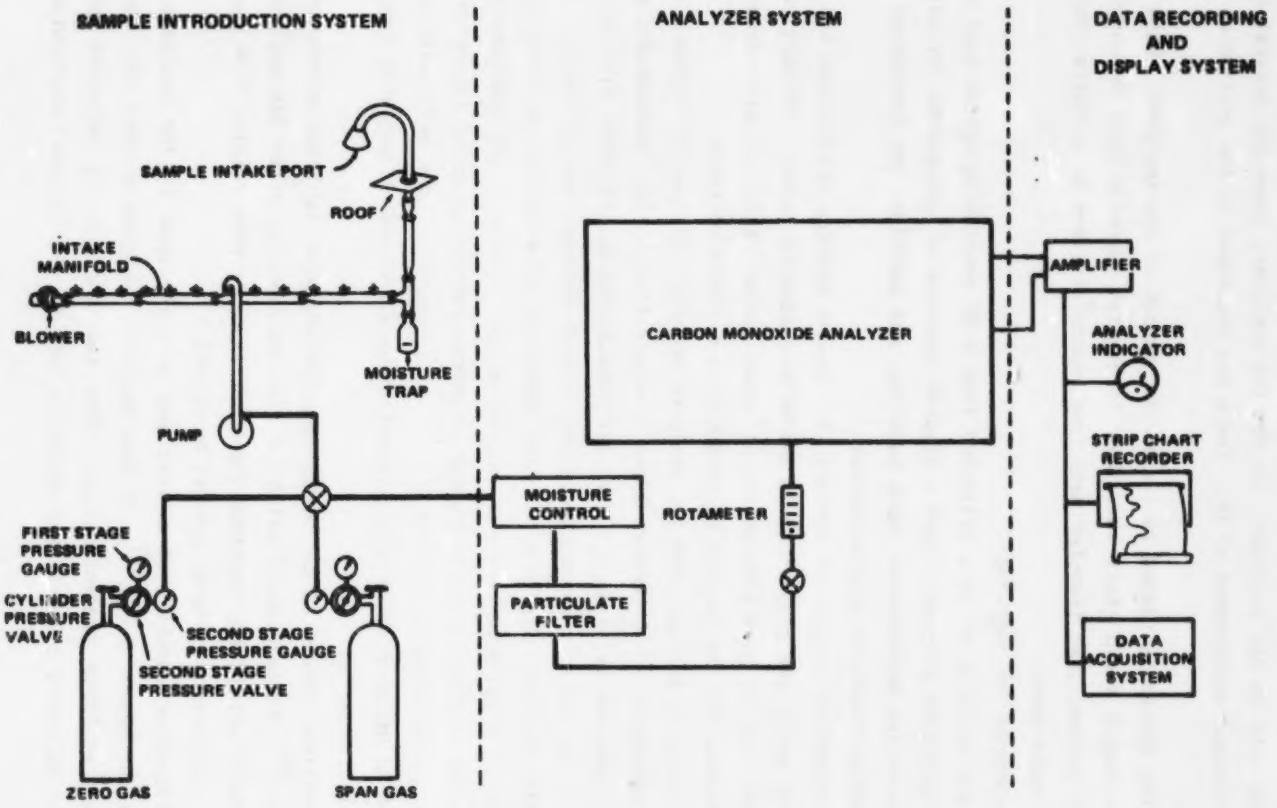

SAMPLE INTRODUCTION SYSTEM
ANALYZER SYSTEM
DATA RECORDING
AND
DISPLAY SYSTEM
SAMPLE INTAKE PORT
ROOF
INTAKE
MANIFOLD
BLOWER
MOISTURE
TRAP
PUMP
FIRST STAGE
PRESSURE
GAUGE
CYLINDER
PRESSURE
VALVE
SECOND STAGE
PRESSURE GAUGE
SECOND STAGE
PRESSURE VALVE
ZERO GAS
SPAN GAS
MOISTURE
CONTROL
PARTICULATE
FILTER
ROTAMETER
CARBON MONOXIDE ANALYZER
AMPLIFIER
ANALYZER
INDICATOR
STRIP CHART
RECORDER
DATA
ACQUISITION
SYSTEM

Figure 5-2. Carbon monoxide monitoring system.[174]

The sample preconditioning system may also include a flow metering and flow control device to control the sampling rate to the analyzer. As for the analyzer, there are several analytical methods for the continuous measurement of CO. These are described in the section on Continuous Measurement Methods.

A data recording system is needed to record the output of the analyzer. Data recording systems range from simple strip chart recorders to digital magnetic tape recorders to computerized telemetry systems that transfer data from remote stations to a central location via telephone lines or radio waves.

Quality Control Procedures for Sampling

The accuracy and validity of data collected from a CO monitoring system must be ensured through a quality assurance program. Such a program consists of procedures for calibration, operational and preventive maintenance, data handling, and auditing; the procedures are fully documented in a quality assurance program manual.

Calibration procedures consist of periodic multipoint primary calibration and secondary calibration, both of which are prescribed to minimize systematic error. Primary calibration involves the introduction of test atmospheres of known concentration to an instrument in its normal mode of operation for the purpose of producing a calibration curve.

A calibration curve is derived from the analyzer response obtained by introducing several successive test atmospheres of different known concentrations. One recommended method for generating CO test atmospheres is to use zero air (containing no CO) along with several known concentrations of CO in air or nitrogen contained in high pressure gas cylinders and verified by NBS-certified SRM wherever possible.[175] The number of standard gas mixtures (cylinders) necessary to establish a calibration curve depends on the nature of the analyzer output. A multipoint calibration at five or six different CO concentrations covering the operating range of the analyzer is recommended by the EPA.[171,177] Alternatively, the multipoint calibration is accomplished by diluting a known high-concentration CO standard gas with zero gas in a calibrated flow dilution system.

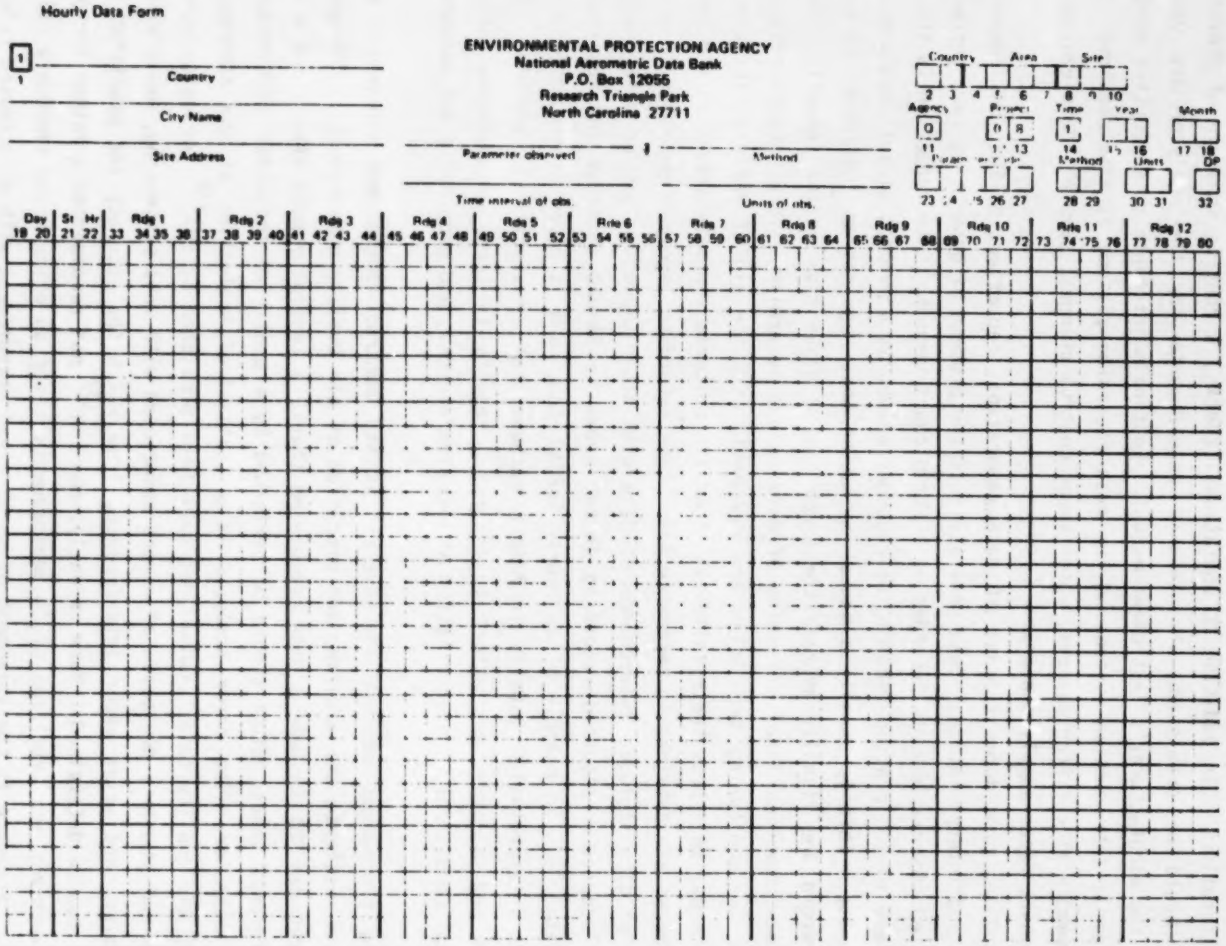
Primary calibrations should be performed when the analyzer is first purchased and every 30 days thereafter.[174] Primary calibration is also recommended after the analyzer has had maintenance that could affect its response characteristics or when results from auditing show that the desired performance standards are not being met.[174]

Secondary calibration consists of a zero and up-scale span of the analyzer. This is recommended to be performed daily.[177] If the analyzer response differs (by more than 2 percent) from the certified concentrations, then the analyzer is adjusted accordingly. Complete records of secondary calibrations should be kept to aid in data reduction and for use in auditing.

Operational and preventive maintenance procedures consist of operational checks to ensure proper operation of the analyzer and a preventive maintenance schedule necessary to prevent unexpected analyzer failure and the associated loss of data.[58] Operational checks include checks of zero and span control settings, sample flow rate, gas cylinder pressures, sample cell pressure, shelter temperature, water vapor control, the particulate filter, the sample introduction system, the recording system, and the strip chart record. These checks may indicate the need for corrective/remedial action. They are usually performed in conjunction with secondary calibrations. In addition to operational checks, a routine schedule of preventive maintenance should be developed. Maintenance requirements for the analyzer are usually specified in the manufacturer's instrument manual. Routine maintenance of supportive equipment (i.e., the sample introduction system and the data recording system) is also required. This may include sample line filter changes, water vapor control changes, sample line cleaning, leak checks, and chart paper supply changes.

Data handling procedures consist of data generation, reduction, validation, recording, and analysis and interpretation. Data generation is the process of generating raw, unprocessed, and unvalidated observations as recorded on a strip chart record. Data reduction is the conversion, by use of calibration records, of recorder output as a percent of full scale to concentration units. This is usually a manual operation that requires an individual to scan a stripchart record and visually average the trace over a given time period (usually 1-hour). Data validation involves final screening of data before recording. Then, questionable data "flagged" by the monitoring technician are reviewed, with the aid of daily calibration and operation records, to assess their validity. Specific criteria for data selection and several instrument checks are outlined in reference 174. Data recording involves recording in a standard format for data storage, interchange of data with other agencies, and/or data analysis. The EPA has adopted a standard recording format known as SAROAD (Storage and Retrieval of Aerometric Data).[173] An example of an hourly SAROAD data form is given in Figure 5-3. Data analysis and interpretation usually include a mathematical or statistical analysis of air quality data and a subsequent effort to interpret results in terms of exposure patterns, meteorological conditions, characteristics of emission sources, and geographic and topographic conditions.

Auditing procedures consist of several quality control checks and subsequent error analyses to an estimate the accuracy and precision of air quality measurements. The quality control checks for CO include a data processing check, a control sample check, and a water vapor interference check, which should be performed by a qualified individual independent of the regular operator. The error analysis is a statistical evaluation of the accuracy and precision of air quality data. Guidelines have been published by EPA[174] for calculating an overall bias and standard deviation of errors associated with data processing, measurement of control samples, and water vapor interference, from which the accuracy and precision of CO measurements can be determined. More recently, the EPA[177] has recommended a method for determining the accuracy and precision of CO measurements based on primary and secondary calibration records. Accuracy is the agreement of an observed measurement with an accepted reference or true value and can be estimated on the basis of multipoint calibration records. Precision is a measure of repeatability and can be estimated from secondary calibration records.



Hourly Data Form

1 1

Country

City Name

Site Address

ENVIRONMENTAL PROTECTION AGENCY
National Aerometric Data Bank
P.O. Box 12055
Research Triangle Park
North Carolina 27711

Parameter observed

Method

Time interval of obs.

Units of obs.

Country 2 3 | Area 4 5 6 7 | Site 8 9 10

Agency 0 11 | Project 0 8 12 13 | Time 1 14 | Year 15 16 | Month 17 18

Parameter code 23 24 25 26 27 | Method 28 29 | Units 30 31 | DP 32

Day	St	Hr	Rdg 1	Rdg 2	Rdg 3	Rdg 4	Rdg 5	Rdg 6	Rdg 7	Rdg 8	Rdg 9	Rdg 10	Rdg 11	Rdg 12
19 20	21	22	33 34 35 36	37 38 39 40	41 42 43 44	45 46 47 48	49 50 51 52	53 54 55 56	57 58 59 60	61 62 63 64	65 66 67 68	69 70 71 72	73 74 75 76	77 78 79 80

Figure 5-3. SAROAD hourly data form.[173]

In summary, the data provided by the quality control checks and subsequent error analyses are sufficient to provide an overall estimate of data quality and an indication that data quality may be inadequate. If the data quality is not adequate, the causes of large deviations should be determined and appropriate action taken to correct the deficiencies. These actions may include an increased auditing program, increased frequency of primary calibrations, increased frequency of preventive maintenance, changes in monitoring procedures, replacement of analyzer, and/or personnel changes.

Sampling Schedules

Carbon monoxide concentrations in the atmosphere exhibit large temporal variations due to changes in the time and rate that CO is emitted by different sources and due to changes in meteorological conditions that govern the amount of transport and dilution that take place. During a one-year period an urban CO station may monitor hourly concentrations of CO ranging from 0 to as high as 50 mg/m^3 (45 ppm). Violations of the NAAQS are based on the second highest 1-hour and 8-hour average concentration, which represents an isolated and "rare" event when compared to the 8760 hours that constitute 1 year. In order to measure this "rare" event, the "best" sampling schedule to employ is continuous monitoring 24-hours per day, 365 days per year. Even so, continuous monitors rarely operate for long periods without data losses due to malfunctions, upsets, and routine maintenance. Data losses of 5 to 10 percent (438 to 876 hours per year) are not uncommon. Consequently, the data must be interpreted in terms of the "likelihood" that the NAAQS were attained or violated. Statistical methods can be employed to interpret the results.[10,94]

While continuous monitoring is the "best" sampling schedule, statistically valid sampling can be performed on random or systematic schedules. Most investigations of various sampling schedules have been conducted for particulate air pollution data,[86,121,127] but the same schedules could also be used for CO monitoring. However, NDIR instruments do not perform reliably in intermittent sampling. Akland[3] evaluated particulate data from 6 years of sampling and showed that 1 day's sampling every 2 weeks could be used to obtain annual mean suspended particulate concentrations within an accuracy of 2.9 percent (systematic sampling) to 5.8 percent (random sampling), compared to every day sampling. When samples were collected every 3 days, the precision was improved to 0.2 percent and 3.9 percent for the systematic and random methods, respectively. The systematic method uses a regular sampling interval of any number of days except seven or multiples of seven. This ensures that all days of the week are sampled equally. Random selection is more likely to result in a less precise yearly estimate than systematic sampling because of daily fluctuations in the units within the sampling interval.[3] Systematic sampling tends to be more representative.

For any number of air samples, the expected deviation of the sample mean from the true population mean can be determined by statistical techniques such as those described by Saltzman.[142] These methods can be used a priori to determine the number of samples it would be desirable to collect during a study. Ott[121] has shown that annual mean CO concentrations can be measured with an accuracy of ±2.16 mg/m^3 (±1.94 ppm), at 0.99 confidence level, with as few as nine random 1-hour average samples during the year (based on data from San Jose, California). With 144 random 1-hour samples, the accuracy was improved to ±0.54 mg/m^3 (±0.49 ppm). The annual mean concentration at this site was 3.93 mg/m^3 (3.54 ppm). With random sampling techniques and automatic bag samplers filling one bag each hour, CO measurements can be made at many more locations and at less cost than continuous monitoring. Ott[121] estimates the cost of random sampling at nine sites to be 70 percent less expensive than continuous monitoring at the same sites.

Short-term studies designed to sample during "worst case" seasons and/or times of day can provide data needed on maximum 1-hour and 8-hour CO concentrations for comparison to NAAQS. In other cases, where concentration trends are not known and where CO concentrations are expected to be high, a full year of data may be necessary.

Recommended Analytical Methods for Carbon Monoxide Measurement

Different analytical methods for CO measurement are required for different purposes, depending on the concentrations to be measured and the physical environment to which the analyzer will be exposed (i.e., temperature, vibration, etc.). When very low global background concentrations are being monitored, only the most sensitive analytical methods can be used. However, for monitoring CO in urban atmospheres for the purpose of determining compliance with National Ambient Air Quality Standards (NAAQS), an EPA "reference" or "equivalent" method should be used. Specifications for automated analytical methods for CO measurement have been issued by the EPA (see Table 5-1). The EPA[171] has specified NDIR as the measurement principle for reference methods for determining compliance with the NAAQS for CO. An "equivalent method" can be so designated when an analytical method is shown to produce results equivalent to an approved NDIR method.

Presently, several reference methods using the NDIR principle have been approved for monitoring for NAAQS achievement. No gas chromatographic/flame ionization (GC) methods have been designated as equivalent methods, but some appear to be suitable for such designation. The I_2O_5 coulometric method is considered to be "unacceptable" because of its slow response, sensitivity to temperature, and interferences by mercaptans, hydrogen sulfide, olefins, acetylenes, and water vapor.[172] All other methods not specifically designated automatically fall under the "unapproved" category. Current lists of designated reference and equivalent methods of analysis for air pollutants can be obtained from EPA regional offices.

Monitoring of CO for purposes other than NAAQS compliance, such as atmospheric research, industrial hygiene, or stack sampling, may employ other methods that may be more sensitive to low CO concentrations, or more suitable to the rigors of field studies. Instruments employing the NDIR method are very sensitive to vibration, which makes them unsuitable for mobile or even portable use. The physical size and usual construction of both NDIR and GC instruments limit their application primarily to laboratory environments.

TABLE 5-1. PERFORMANCE SPECIFICATIONS FOR AUTOMATED ANALYTICAL METHODS FOR CARBON MONOXIDE[175]

Range	0 to 57 mg/m^3 (0 to 50 ppm)
Noise	0.6 mg/m^3 (0.50 ppm)
Lower detectable limit	1.2 mg/m^3 (1.0 ppm)
Interference equivalent	
Each interfering substance	±1.2 mg/m^3 (±1.0 ppm)
Total interfering substances	1.7 mg/m^3 (1.5 ppm)
Zero drift	
12-hr	±1.2 mg/m^3 (±1.0 ppm)
24-hr	±1.2 mg/m^3 (±1.0 ppm)
Span drift, 24 hr	
20 percent of upper range limit	±10.0 percent
80 percent of upper range limit	± 2.5 percent
Lag time	10 min.
Rise time	5 min.
Fall time	5 min.
Precision	
20 percent of upper range limit	0.6 mg/m^3 (0.5 ppm)
80 percent of upper range limit	0.6 mg/m^3 (0.5 ppm)

Definitions:

Range: Nominal minimum and maximum concentrations that a method is capable of measuring.

Noise: The standard deviation about the mean of short duration deviations in output that are not caused by input concentration changes.

Lower Detectable Limit: The minimum pollutant concentration that produces a signal of twice the noise level.

Interference Equivalent: Positive or negative response caused by a substance other than the one being measured.

Zero Drift: The change in response to zero pollutant concentration during continuous unadjusted operation.

Span Drift: The percent change in response to an up-scale pollutant concentration during continuous unadjusted operation.

Lag Time: The time interval between a step change in input concentration and the first observable corresponding change in response.

Rise Time: The time interval between initial response and 95 percent of final response.

Fall Time: The time interval between initial response to a step decrease in concentration and 95 percent of final response.

Precision: Variation about the mean of repeated measurements of the same pollutant concentration expressed as one standard deviation about the mean.

Portable instruments are commercially available for making CO measurements in the field by different analytical techniques. Instruments based on controlled-potential electrochemical analysis have detection limits of less than 1 mg/m^3 (0.9 ppm).[13,20] These instruments can be employed for portable measurements in mines and hostile working environments, as well as in research for commuter "in-car" exposure,[45] indoor worker exposure,[45] or CO measurements taken from aircraft. Another common technique for obtaining intermittent CO concentration data is to employ portable pumps and air sampling bags to collect an air sample that can be later analyzed for CO concentration by NDIR or another method.[38,120] Bags of 2 to 90 liters are typical. Construction materials include Mylar®, Tedlar®, aluminized Scotch-pak®, Scotch-pak®, Saran®, and Teflon®.[6,147] The inert properties of CO make it ideal for bag sampling, since the in-bag rate of decay is slow. However, investigators using the bag sampling technique should perform their own tests of decay rate as part of their quality assurance program.

Grab samples from stacks or automobile exhaust pipes, in which CO concentrations may range from 500 mg/m^3 (450 ppm) to several percent CO, may be analyzed with colored silver sols detection tubes[6,38] or by Orsat analysis. Bag samples of these exhaust gases can also be taken, quantitatively diluted, then analyzed by an NDIR instrument.[38]

Continuous Measurement Methods

Non-dispersive Infrared Photometry--Carbon monoxide has a characteristic infrared absorption near 4.6 μm; the absorption of infrared radiation by the CO molecule therefore can be used to measure CO concentration in the presence of other gases. The NDIR method is based on this principle.

Although the size, shape, sensitivity, and range of NDIR instruments vary with manufacturer, their basic components and configurations are similar. Most commercially available instruments include a hot filament source of infrared radiation, a rotating sector (chopper), a sample cell, a reference cell, and a detector (see Figure 5-4).

The reference cell contains a non-infrared-absorbing gas, while the sample cell is continuously flushed with the sample atmosphere. The detector consists of a two-compartment gas cell (both filled with CO under pressure) separated by a diaphragm whose movement causes a change of electrical capacitance in an external circuit and ultimately an amplified electrical signal suitable for input to a servo-type recorder.

During analyzer operation an optical chopper intermittently exposes the reference and sample cells to the infrared sources. At the frequency imposed by the chopper, a constant amount of infrared energy passes through the reference cell to one compartment of the detector cell while a varying amount of infrared energy, approximately inversely proportional to the CO concentration in the sample cell, reaches the other detector cell compartment. These unequal amounts of residual infrared energy reaching the two compartments of the detector cell cause unequal expansion of the detector gas, resulting in variation in the detector cell diaphragm movement, which in turn produces the electrical signal previously discussed.

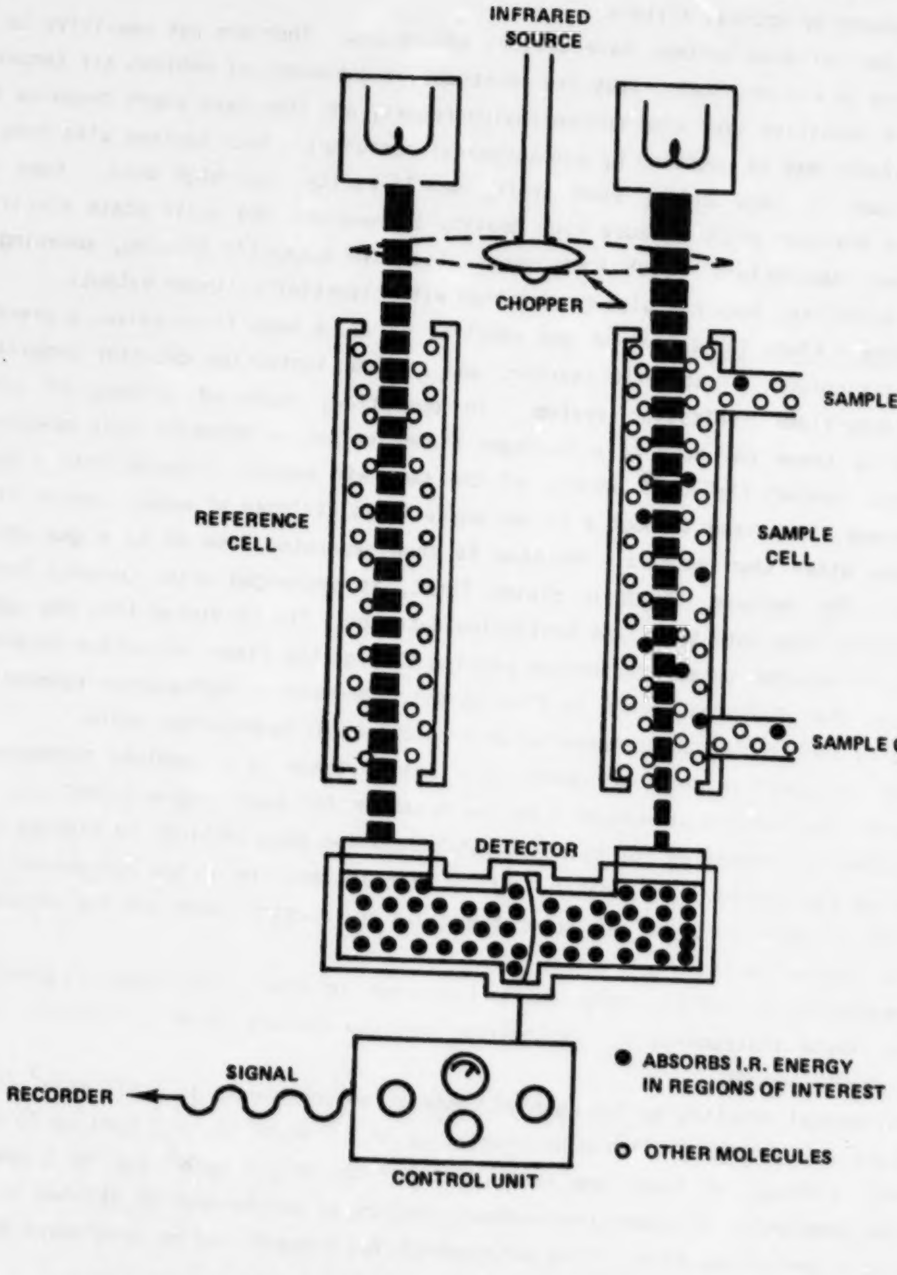

INFRARED SOURCE
CHOPPER
REFERENCE CELL
SAMPLE CELL
SAMPLE IN
SAMPLE OUT
DETECTOR
SIGNAL
RECORDER
CONTROL UNIT
● ABSORBS I.R. ENERGY IN REGIONS OF INTEREST
O OTHER MOLECULES

Figure 5-4. Schematic diagram of typical nondispersive infrared CO analyser.[58]

Because water vapor is the principal interfering substance in determining CO by NDIR techniques, a moisture control system is particularly important. To reduce water vapor, which gives an erroneously high value, water can be removed by drying agents or cooling, or its effect can be reduced by optical filters.

Non-dispersive infrared systems have several advantages. They are not sensitive to flow rate, they require no wet chemicals, they are reasonably independent of ambient air temperature changes, they are sensitive over wide concentration ranges, and they have short response times. Further, NDIR systems may be operated by non-technical personnel. Such systems also have some disadvantages, such as zero drift, span drift, non-linearity, and high cost. Some newer instruments have minimum drift because high quality thermostats and solid state electronics are used in their manufacture. Such instruments also have automatic zeroing, spanning, and recalibrating capability; they may also be obtained with essentially linear outputs.

Gas Chromatography - Flame Ionization--A gas sampling valve, a back flush valve, a precolumn, a molecular sieve column, a catalytic reactor, and a flame ionization detector comprise the gas chromatography-flame ionization system. In operation, measured volumes of air are delivered 4 to 12 times per hour to a hydrogen flame ionization detector that measures the total hydrocarbon content (THC). A portion of the same air sample, injected into a hydrogen carrier gas stream, is passed through a column where it is stripped of water, carbon dioxide, and hydrocarbons other than methane. Methane is then separated from CO by a gas chromatographic column. The methane, which is eluted first, is unchanged after passing through a catalytic reduction tube into the flame ionization detector. The CO eluted into the catalytic reduction tube is reduced to methane before passing through the flame ionization detector.[130] Between analyses the stripping column is flushed out. Nonmethane hydrocarbon concentrations are determined by subtracting the methane value from the total hydrocarbon value.

There are two possible modes of operation. One of these is a complete chromatographic analysis showing the continuous output from the detector for each sample injection. In the other, the system is programmed for both automatic zero and span settings to display selected elution peaks as bar graphs. The peak height is then the measure of the concentration. The first operation is referred to as the chromatographic or "spectro" mode and the second as the barographic or "normal" mode.

Since measuring CO entails only small increases in cost, instrument complexity, and analysis time, these instruments are customarily used to measure three pollutants: methane, total hydrocarbons, and CO.

The instrumental sensitivity for each of these three components is 0.023 mg/m^3 (0.02 ppm). The lowest full-scale range available is usually up to 2.3 mg/m^3 (0 to 2 ppm) up to 5.7 mg/m^3 (up to 5 ppm), although at least one instrument has up to 1.2 mg/m^3 (up to 1 ppm) range. Because of the complexity of these instruments, continuous maintenance by skilled technicians is required to minimize downtime. This maintenance requirement may be considered a possible disadvantage of the system.

Electrochemical Analyzers

Controlled-potential electrochemical analysis. Carbon monoxide is measured by means of the current produced in aqueous solution by its electro-oxidation at a catalytically active electrode. The concentration of CO reaching the electrode is controlled by its rate of diffusion through a membrane. This is dependent on its concentration in the sampled atmosphere.[12,13] Proper selection of both the membrane and such cell characteristics as the nature of the electrodes and the solutions make the technique selective for various pollutants. A similar technique has been reported by Yamate and Inoue.[194]

The generated current is linearly proportional to the CO concentration from 0 to 115 mg/m^3 (0 to 100 ppm). A sensitivity of 1.2 mg/m^3 (1 ppm) and a 10-second response time (90 percent) are claimed for a currently available commercial instrument.

Acetylene and ethylene are the chief interfering substances: 1 part acetylene responds as 11 parts CO, and 1 part ethylene as 0.25 part CO. For hydrogen, ammonia, hydrogen sulfide, nitric oxide, nitrogen dioxide, sulfur dioxide, natural gas, and gasoline vapor, interference is less than 0.03 part CO per 1 part interfering substance.

Galvanic analyzer. Galvanic cells employed in the manner described by Hersch[76,77] can be used to measure atmospheric CO continuously. When an air stream containing CO is passed into a chamber packed with I_2O_5 and heated to 150°C, the following reaction takes place:

$$5CO + I_2O_5 \xrightarrow{(150^\circ C)} 5CO_2 + I_2.$$

The liberated iodine is absorbed by an electrolyte and transferred to the cathode of a galvanic cell. At the cathode, the iodine is reduced and the resulting current is measured by a galvanometer. Instruments with this detection system have been used successfully to measure CO levels in traffic along freeways.[70]

Mercaptans, hydrogen sulfide, hydrogen, olefins, acetylenes, and water vapor interfere. Water may be removed by sampling through a drying column; hydrogen, hydrogen sulfide, acetylene, and olefin interferences can be minimized by sampling through an absorption tube containing mercuric sulfate on silica gel.

Coulometric analyzer. A coulometric method employing a modified Hersch-type cell has been used for continuous measurement of CO in ambient air.[57] The reaction of I_2O_5 with CO liberates iodine, which is then passed into a Ditte cell, and the current generated is measured by an electrometer-recorder combination. Interferences are the same as those discussed above for the galvanic analyzer.

This technique may be used for a minimum detectable concentration of 1.2 mg/m^3 (1 ppm) with good reproducibility and accuracy if flow rates and temperatures are well controlled. This method requires careful column preparation and use of filters to remove interferences. Its relatively slow response time may be an added disadvantage in some work.

Mercury Replacement--Mercury vapor formed by the reduction of mercuric oxide by CO is detected photometrically by its absorption of ultraviolet light at 253.7 nm. The reaction involved is:

$$CO + HgO \xrightarrow{(210^\circ C)} CO_2 + Hg$$

This is potentially a much more sensitive method than infrared absorption because the oscillator strength of mercury at 253.7 nm is 2000 times greater than that of CO at 4.6 µm. Hydrogen and hydrocarbons also reduce mercuric oxide to mercury, and there is some thermal decomposition of the oxide. Operation of the detector at constant temperature results in a regular background concentration of mercury from thermal decomposition. The instrument is portable and can analyze CO concentrations of 0.025 to 12 mg/m^3 (0.020 to 10.0 ppm). Changes of 0.002 mg/m^3 (0.002 ppm) are detectable. For this reason, this instrument has been used to determine global CO levels.

McCullough et al.[14,110] recommended a temperature of 175°C to minimize hydrogen interference. A commercial instrument employing these principles was made and used during the middle 1950s.[115] The technique has recently been used for measuring background CO concentrations. Robbins et al.[138] have described an instrument in which the mercuric oxide chamber is operated at 210°C, and the amount of hydrogen interference is assessed by periodic introduction of a tube of silver oxide into the intake air stream. At room temperature silver oxide quantitatively oxidizes CO, but not hydrogen. Thus, the baseline hydrogen concentration can be determined. Additional minor improvements are discussed by Seiler and Junge,[150] who gave the detection limit for CO as 0.003 mg/m^3 (0.003 ppm).

More recently, Palanos[123] described a less sensitive model of this instrument intended for use in urban monitoring. It has a range of 0 to 23 mg/m^3 (20 ppm), a sensitivity of about 0.58 mg/m^3 (0.5 ppm), and a span and zero drift of less than 2 percent per day. As in other similar instruments, specificity is achieved by removal of the potentially interfering substances (which is less than 10 percent) other than hydrogen.

All of these instruments assume a constant hydrogen concentration. In unpolluted atmospheres, the hydrogen concentration is roughly 46.5 $\mu g/m^3$ (0.56 ppm). However, the automobile is not only a source of CO but also of hydrogen. Therefore, if this technique is used in polluted areas, it will be necessary to measure the hydrogen concentration frequently.

Dual Isotope Fluorescence--This instrumental method utilizes the slight difference in the infrared spectra of isotopes. The sample is alternately illuminated with the characteristic infrared wavelengths of carbon monoxide-16 (CO^{16}) and carbon monoxide-18 (CO^{18}). The CO in the sample that has the normal isotope ratio, nearly 100 percent CO^{16}, absorbs only the CO^{16} wavelengths. Therefore, there is a cyclic variation in the intensity of the fluorescent light that is dependent on the CO^{16} content of the sample.[101,107,108]

Full-scale ranges of 0 to 23 mg/m^3 (0 to 20 ppm) and up to 0 to 230 mg/m^3 (0 to 200 ppm) with a claimed sensitivity of 0.23 mg/m^3 (0.2 ppm) are available in this instrument. The response time (90 percent) is 25 seconds, but a 1-second response time is also available. An advantage of this technique is that it minimizes the effects of interfering substances.

Catalytic Combustion - Thermal Detection--Determination of CO by this method is based on measuring the temperature rise resulting from catalytic oxidation of the CO in the sample air.

The sample air is pumped first into a furnace that brings it to a pre-set, regulated temperature and then over the catalyst bed in the furnace. A thermopile assembly measures the temperature difference between the air leaving the catalyst bed and the air entering it. The output of the thermopile, which is calibrated with known concentrations of CO in air, is read on a strip-chart recorder as parts of CO per million parts of air. The sensitivity is about 1.2 mg/m^3 (1 ppm). Most hydrocarbons are oxidized by the same catalyst, and will interfere unless removed. These systems are widely used in enclosed spaces; their applicability for ambient air monitoring is limited because they function best at high ambient concentrations.

Second-Derivative Spectrometry--A second-derivative spectrometer processes the transmission versus wavelength function of an ordinary spectrometer to produce an output signal proportional to the second derivative of this function. Ultraviolet light of continuous wavelength is collected and focused onto an oscillating entrance slit of a grating spectrometer. When the grating orientation is changed slowly, a slowly scanning center wavelength with sinusoidal wavelength modulation is created in the existing light by the oscillating entrance slit. This radiation passes through a gas sample and is detected with a photomultiplier tube. The signal is then electronically processed to produce a second-derivative spectrum.[96] This method has the advantage that it can be used to measure other pollutants as well as CO. Commercial instruments are currently under development.

Fourier Transform Spectroscopy--Fourier transform spectroscopy is an extremely powerful infrared spectroscopic technique[16] that has developed in the past 20 years and has been applied in the last 10 years to air pollution measurement problems.[72,96] The advantages of this technique over a standard grating or prism spectrometer are that it has a higher through-put, which means that the available energy is used more effectively and that a much higher resolving power is obtainable. In air pollution measurements individual absorption lines can be resolved.

A special advantage for air pollution measurements is that all the data required to reconstruct the entire absorption spectrum are acquired at the same time. The spectrum as a function of wavelength is generated by a built-in computer. This means that several gases can be measured simultaneously. Several commercial instruments are now available with resolutions of 0.06/cm or better. These instruments are capable of clearly defining the spectra of any gaseous pollutant, including CO and are currently being used for special air pollution studies.

Gas Filter Correlation Spectroscopy--A gas filter correlation (GFC) monitor[25] is in essence a modern NDIR monitor, but it has not been defined as such by EPA. It has all the advantages of an NDIR instrument and the additional advantages of smaller size, no interference from CO_2, and very small interference from water vapor. It is not sensitive to flow rate, requires no wet chemicals, has a very fast response, and is independent of normal ambient temperature changes. There is a problem with zero drift, but not with span drift. Furthermore, the instrument has recently been packaged as a portable monitor.

In this instrument, the infrared beam is collimated by a lens before passing through the gas filter, the interference filter, and the sample cell. The signal arises from the difference in amplitude of the signal that alternately passes through one-half of the filter cell containing CO and the other half containing a neutral gas such as N_2 and a neutral filter. The signal is balanced when no CO remains in the sample cell. An increase in CO in the sample cell will increase the difference signal, since the portion of the beam that has already passed through the CO in the gas filter will be unchanged by the CO in the sample cell, whereas the beam passing through the neutral half will be attenuated by the CO in the sample. A prototype version of this monitor had a minimum sensitivity of 50 parts per billion.[27]

Intermittent Analysis

Intermittent samples may be collected in the field and later analyzed in the laboratory by the continuous analyzing techniques described above. Sample containers may be rigid (glass cylinders or stainless steel tanks) or they may be non-rigid (plastic bags). Because of location or cost, intermittent sampling at times may be the only practical method for air monitoring. Samples can be taken over a few minutes or accumulated intermittently to obtain, after analysis, either "spot" or "integrated" results. Additional techniques for analyzing intermittent samples are described below.

Colorimetric Analysis

Colored silver sol method. Carbon monoxide reacts in an alkaline solution with the silver salt of p-sulfamoylbenzoate to form a colored silver sol. Concentrations of 12 to 23,000 mg/m^3 (10 to 20,000 ppm) CO may be measured by this method.[28-32,98] The method has been modified to determine CO concentrations in incinerator effluents. Samples are collected in an evacuated flask and reacted. The absorbance of the resulting colloidal solution is measured spectrophotometrically. Acetylene and formaldehyde interfere, but can be removed by passing the sample through mercuric sulfate on silica gel. Carbon monoxide concentrations of 5.8 to 20,700 mg/m^3 (5 to 18,000 ppm) may be measured with an accuracy of 90 to 100 percent of the true value.

National Bureau of Standards colorimetric indicating gel.
A National Bureau of Standards (NBS) colorimetric indicating gel (incorporating palladium and molybdenum salts) has been devised to measure CO in the laboratory and in the field.[151,152] The laboratory method involves colorimetric comparison with freshly prepared indicating gels exposed to known concentrations of CO. The method has an accuracy range of 5 to 10 percent of the amount of CO involved, and the minimum detectable concentration is 1.2 mg/m^3 (1 ppm). This technique requires relatively simple and inexpensive equipment; however, oxidizing and reducing gases interfere, and the preparation of the indicator tube is a tedious and time-consuming task.

Length-of-stain indicator tube. An indicator tube that uses potassium palladosulfite is a commonly employed manual method.[153] Carbon monoxide reacts with the contents of the tube and produces a discoloration.

The length of discoloration is an exponential function of the CO concentration. This method and other indicator tube manual methods are estimated to be accurate to within ±25 percent of the amount present, particularly at CO concentrations of about 115 mg/m^3 (100 ppm). Such indicator tube manual methods have been used frequently in air pollution studies. Ramsey[132] used the technique to measure CO at traffic intersections, and Brice and Roesler[21] estimated CO concentrations with an accuracy of ±15 percent by means of color-shade detector tubes.

Colorimetric techniques and length-of-stain discoloration methods are recommended for use only when other physicochemical monitoring systems are not available. They may be used in the field for gross mapping where accuracy is not required and may possibly be of great value during emergencies.

Frontal Analysis--Air is passed over an adsorbent until equilibrium is established between the concentration of CO in the air and the concentration of CO on the adsorbent. The CO is then eluted with hydrogen, reduced to methane on a nickel catalyst at 250°C, and determined by flame ionization as methane.

Concentrations of CO as low as 0.12 mg/m^3 (0.10 ppm) can be measured. This method does not give instantaneous concentrations, but does give averages over a 6-minute or longer sampling period.[55,56]

MEASURING CARBON MONOXIDE IN BLOOD

The best index of CO exposure is the carboxyhemoglobin (COHb) percent saturation. Carboxyhemoglobin can be determined satisfactorily on venous blood since the differences found between venous and arterial concentrations have been insignificant. Venous blood should be collected in a closed container (vacutainer tubes are adequate) with an anticoagulant such as dry sodium heparin or sodium ethylene-diaminetetraacetic acid (EDTA). There must be no air trapped in the syringe or container. Blood samples may be preserved for several days prior to analysis if kept in the cold (4°C) and in the dark. Complete mixing of blood must be performed if CO, as a gas, and hemoglobin (Hb) are measured separately. This mixing must assure that the normal hematocrit of the sample is present prior to analysis. Total Hb determination is most conveniently performed by the reaction to form cyanomethemoglobin.[53] A satisfactory procedure is to use the reagent of Van Kampen and Zijlstra[181] with precautions to prevent gradual loss of hydrogen cyanide (HCN) from the acid reagent and to allow sufficient time for total conversion of COHb. Measurements of CO by elaboration of the gas or by non-destructive spectrophotometric procedures have been developed (Table 5-2).

Carbon monoxide combines rapidly with Hb to form COHb, which is much more stable than O_2Hb. This combination decreases the O_2 transport capability of blood, causing O_2 deprivation in tissues and, thus, impaired physiologic status. Therefore, the chemical analysis of blood for its COHb content is an important measure of toxic effect, as well as recent exposure, for CO.

TABLE 5-2. COMPARISON OF REPRESENTATIVE TECHNIQUES FOR ANALYSIS OF CO IN BLOOD[a]

Reference	Method	Sample vol, ml	Resolution,[b] ml/dl	Sample analysis time, min	CV %[c]
GASOMETRIC					
Horvath and Roughton[80]	Van Slyke	1.0	0.03	15	6
Scholander and Roughton[146]	Syringe-capillary	0.5	0.02	30	2-4
OPTICAL					
Coburn, Forster and Kane[36]	Infrared	2.0	0.006	30	1.8
Small et al.[156]	Spectrophotometric	0.1	0.08	10	
Maas, Hamelink and De Leeuw[103]	CO-Oximeter	0.4	0.10	3	
CHROMATOGRAPHIC					
McCredie and Jose[109]	Thermal conductivity	1.0	0.005	20[d]	1.8
Collison, Rodkey and O'Neal[39]	Flame ionization	0.1	0.002	20	1.8
Ayers et al.[9]	Thermal conductivity	1.0	0.001	30	2.0
Dahms & Horvath[47]	Thermal conductivity	0.25	0.006	6.5	1.7

[a] From Dahms and Horvath modified.[47]

[b] Smallest detectable difference between duplicate determinations.

[c] Calculated based on samples containing less than 2.0 ml CO per deciliter.

[d] Best estimate.

The analytical results are usually expressed as the ratio of the concentrations of COHb to total Hb. Human blood has a baseline level of about 0.5 percent of COHb, due to endogenous production of small amounts of CO by catabolic processes. This basal level can be higher at certain times in females, individuals with hemolytic disease, etc. Urban non-smokers show about 1 percent COHb in blood, while moderate smokers show about 5 percent.[166] Parking garage employees have shown levels above 10 percent at the end of the workday.[133]

There are several reviews of analytical procedures for CO in blood;[40,52,61,104] these can be grouped into non-destructive, destructive, and equilibrium methods.

If the COHb concentration is measured as such in solution, the method is non-destructive; if the complex is destroyed in order to liberate the CO gas for measurement, the method is destructive.

Other Methods

The intense color of Hb and its complexes suggests the use of spectrophotometry as a non-destructive analytical tool. Very strong Soret absorption peaks in the 410 to 435 nm region, as well as moderately strong peaks in the 520 to 600 nm region, are shown by reduced Hb, COHb, O_2Hb, Methemoglobin (MetHb), and other Hb derivatives.[53,90,131,156] Even though the spectrophotometric curves are distinctive for each compound, they overlap so much that it is not possible to measure quantitatively or isolate one component (such as COHb) in a mixture by a simple measurement of absorbance at a wavelength where that component absorbs light and other Hb derivatives do not.

A systematic procedure in such situations is to (1) determine the absorptivity of each pure compound at each of several carefully selected wavelengths; (2) measure the absorbance of the unknown mixture at each of the wavelengths; and (3) separate the contribution of each pure compound by solving a set of simultaneous equations that contain coefficients for the individual absorptivities at each wavelength. A high-precision spectrophotometer with excellent wavelength stability and resolution is needed.

An example of this approach is Small's method.[156] After dilution of blood 1:70 with 0.04 percent ammonia solution, the absorbance is measured at four wavelengths in the Soret region. From a set of simultaneous equations containing these measured values, calculations yield the percent COHb, percent Methemoglobin, and percent O_2Hb. The stated error is ±0.6 percent COHb at concentrations of 25 percent COHb or lower. This margin provides ample accuracy at high levels, but makes the method less useful at low levels of around 1 percent COHb or less. A related technique[105] is the basis for a commercial instrument, the CO-Oximeter model 282 (Instrumentation Laboratory, Inc., Lexington, MA), which uses four wavelengths outside the Soret region and includes a small computer for performing the calculations, yielding percentages of total Hb as well as of COHb, O_2Hb, and MetHb. CO-Oximeters are used widely,[103,122] but require careful calibration at COHb concentrations below 5 percent. This comparison was made against a CO-X model 182, and the discrepancy at low COHb is correct, but it is not known how this related to the model 282.[140]

An earlier method by Amenta[5] is similar in principle and also uses wavelengths outside the Soret region: 498 nm (an isosbestic point), 560 nm, and 575 nm. The percent COHb results obtained in the low concentration range have a precision of only 10 percent.

Other spectrophotometric methods include some chemical treatments.[73,90] In Klendshoj's procedure, oxalated blood is first diluted 1:100 with 0.4 percent ammonia; then sodium dithionite ("hydrosulfite") is added and the absorbance is measured at 480 nm and 555 nm. After dithionite treatment, the only Hb species present are reduced Hb and COHb. These two have the same absorptivity at 555 nm, but different absorptivities at 480 nm; the ratio A_{555}/A_{480} decreases with increased COHb concentration. A calibration curve is prepared from known standards; certain precautions are needed in making up such standards.[193] Klendshoj's method is simple, rapid, and accurate enough to measure a 2 percent change in COHb concentration. However, at low levels, the method is less useful.

Another spectrophotometric method makes use of the fact that O_2Hb is much more readily precipitated than COHb when heated 8 minutes at 57°C.[190] After the solution is filtered and cooled, the change in absorbance at 555 nm is measured and the COHb content of the blood is measured by calibrating the method with standard solutions of known concentration. The procedure is simple, but not very sensitive or accurate.

In the differential spectrophotometric technique of Commins and Lawther,[41] an aqueous solution of the blood sample is divided equally and oxygen is bubbled through one half of the solution for 15 minutes to convert any COHb into O_2Hb. The spectra of the two halves are then compared and the difference between them (together with a measurement of Hb in the oxygenated portion) is used to find the COHb content of the blood. This method is said to be capable of detecting 0.2 percent COHb in blood, and has shown good agreement with two different destructive methods for COHb analysis.[23]

Double wavelength spectrophotometry is used in a recently developed rapid method for COHb.[131] Two monochromators in the same instrument send light beams of different wavelengths alternately through a single cuvette; the difference in absorbance is measured by the photometer. The carefully chosen wavelengths are 530.6 nm and 583.0 nm, at which O_2Hb has equal absorptivities, and also at which reduced Hb has equal absorptivities. Any difference in absorbance found is due to the presence of COHb, which has unequal absorptivities at the two wavelengths. As with all such methods, careful calibration with known samples is required. The procedure has acceptable accuracy at levels of a few percent of COHb, but MetHb causes interference.

Infrared spectrophotometry of CO bound to Hb can be performed directly on blood and other tissues, and holds promise as a specific method for COHb analyses. An exploratory study used measurements at 1951 cm^{-1} in CaF_2 cells having 0.05 mm optical pathlength.[106]

Other possible spectrometric techniques for COHb analysis include Mossbauer (which requires a solid sample, such as frozen blood), carbon-13 nuclear magnetic resonance, and electron spin resonance. These offer some promise of specificity, but are far from being developed into usable methods.

A different approach to COHb analysis is to decompose the complex and measure the amount of CO gas released. Such liberation of CO has been carried out by addition of various acids (hydrochloric, sulfuric, phosphoric, acetic, citric, lactic) and/or oxidizing agents such as potassium ferricyanide or potassium hydrogen iodate. These methods tend to have the disadvantage of requiring (1) larger samples of blood than for spectrophotometry, and (2) a separate analysis for total concentration of Hb, if the percent COHb is needed.

Of the many analytical methods available for gaseous CO, several are noted briefly below.

Gasometric--The Van Slyke method and its modifications[80,182,183] measure the volume or the pressure of the CO gas present.[159] Historically, these were macro methods and not of high sensitivity, but successful micro procedures have been developed.[141,146] They require considerable skill and are time-consuming.

Infrared Spectrometry--Carbon monoxide has a characteristic infrared absorption near 4.6 μm. This is widely used for analysis, especially with non-dispersive instruments as in the EPA reference method for atmospheric monitoring. In this method, the absorption due to any CO present is measured by its differential heating effect and resulting displacement of a flexible diaphragm that is one element of a capacitance detector. Methods using NDIR for COHb analysis in blood are available.[35,63,189] Water vapor interferes unless its concentration is carefully controlled.

Catalytic Oxidation--Like NDIR, this method has enough sensitivity and accuracy to detect small changes in COHb concentration. The liberated CO can be oxidized by a catalyst such as Hopcalite and the temperature rise caused by this exothermic reaction measured with a thermopile or quartz crystal.[100,117,129,163]

Electrochemical Sensors--Another analytical technique based on oxidation of CO is electrochemical. In a special electrode, the gas sample is allowed to diffuse through a Teflon membrane bearing a thin film of catalytically active metal (such as platinum) on the far side, in contact with the electrolyte. At a controlled applied potential, the current flow is determined by the CO concentration in the gas.[13,17,18,20,34,50] A different electrical procedure for analysis of CO is to measure the change in conductivity it causes when adsorbed by semiconductors such as metal oxides.[62,95]

Gas Chromatography--The chromatographic separation of CO from other blood gases is readily accomplished by a molecular sieve.[9,47,51,78,91] To achieve greater sensitivity than that given by a thermal conductivity detector, a flame ionization detector can be used in the gas chromatograph if the CO is first catalytically reduced to methane, in-line after its separation by the molecular sieve.[39,130,139,192]

Colorimetric palladium chloride reaction--In a Conway microdiffusion cell,[93] CO released from blood diffuses into a solution of palladium (II) chloride, which is reduced to metallic palladium. The excess $PdCl_2$ is determined colorimetrically, by conversion to the pinkish iodide complex[4] or by formation of a violet complex with promazine.[88] Another colorimetric reagent for CO is a mixture of palladium and molybdenum compounds.[92,99]

Equilibrium Methods

If equilibrium can be established between blood gases and lung gases, then analysis of exhaled air will give a measure of COHb blood levels.[26,60,126,134,155,185] The relationship is

$$[\mathrm{COHb}] = M\,[\mathrm{O_2Hb}]\,\frac{p_{CO}}{p_{O2}}\ ,$$

where p_{O_2} is the partial pressure of O_2 in the pulmonary blood; p_{CO} is the measured partial pressure of CO in the exhaled air; the bracketed quantities are the blood concentrations of COHb and O_2Hb, respectively; and M is the ratio of the stability constant of COHb to that of O_2Hb. The Haldane constant, M,[71] has a numerical value of about 220 to 250 for human beings at physiological pH and body temperature.[36,140]

The alveolar air method should be used in epidemiological studies only with extreme care. Hoover and Albrecht,[79] in their study of driving in New York City traffic, reported that CO concentrations in alveolar air did not correlate acceptably with measurements of COHb. The equilibrium method cannot be used in people with chronic lung disease, because their alveolar gas composition can be quite variable. Even healthy subjects need special training in the method to obtain valid results.

In this method, the main problem is to approach equilibrium conditions even though the composition of lung gas is changing continually during normal respiration. One solution is breath-holding. When a subject holds his breath, the alveolar concentration of CO increases initially as CO diffuses out of the blood toward equilibrium.[7,19,36,48,89,137] However, as the alveolar O_2 content decreases, some of the CO is reabsorbed into the blood. The optimum time period for breath-holding has been found to be 20 seconds.

The standard technique is for the subject to expel air from the lungs maximally, then breathe in as far as possible, hold his breath for 20 seconds, and then exhale as far as possible. The first 500 ml of expired air is discarded, and the remainder is collected in a gas-tight bag for CO analysis by a reliable method. A rugged instrument for field use, as for measuring COHb in firefighters, is the Ecolyzer, which measures CO by electrochemical oxidation at a Teflon®-bonded diffusion anode.[165]

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6. OBSERVED CARBON MONOXIDE CONCENTRATIONS

Ambient concentrations of carbon monoxide (CO) in urban communities vary widely with time and space. Human exposure patterns of CO are complex, but they can be discerned from ambient air measurements and the estimates of computer models. This chapter presents some typical results of continuous air monitoring of CO that provide a better understanding of CO exposure problems. In addition to describing observed diurnal, seasonal, and annual patterns of ambient urban CO levels, this chapter explains the importance of air monitoring site selection, of meteorological and geographic effects on CO exposures, techniques of CO trend analyses, and special CO exposure situations. Also provided is an overview of meteorological diffusion models.

SITE SELECTION

Site selection is one of the most complex and critical elements in the design of CO air monitoring programs. If the "wrong" monitoring sites are chosen, or if a critical (i.e., high concentration) site is missed, no amount of accurate data from other sites will suffice to meet the objectives of the monitoring program. Naturally, the choice of monitoring sites depends greatly on the objective of the monitoring to be performed. The EPA[70] recognizes the following as general objectives for monitoring:

1. To judge compliance with and/or progress made toward meeting ambient air quality standards.
2. To activate emergency control procedures to prevent air pollution episodes.
3. To observe pollution trends throughout the region, including the non-urban areas. (Information from non-urban areas is needed to evaluate whether air quality in the cleaner portions of a region is deteriorating significantly and to gain knowledge about background pollutant levels.)
4. To provide a data base for application in the evaluation of effects; in urban, land use, and transportation planning; in development and evaluation of abatement strategies; and in development and validation of diffusion models.

As well as being used on monitoring objectives, sites selection is also based on the scale of representativeness that will meet the objectives. Data representativeness, like measures of concentration at a site, is dependent on the proximity of the monitor to the CO source. Ground level concentrations of CO within an urban area vary widely because the principal source of CO in cities is automobiles, which, obviously, move and are more concentrated in some areas at some times than at other times. Monitoring sites at the edge of a highway will measure CO concentrations representative of a fairly small area. Sites well removed from highways can be representative of a fairly large-scale air mass. The EPA[84] has defined six scales of spatial representativeness for CO monitoring sites: microscale, middle-scale, neighborhood-scale, urban-scale, regional-scale, and national- and global-scale.

Most CO monitoring conducted in the United States is for the purpose of determining attainment or nonattainment of air quality standards. Since monitoring resources have been and continue to be severely limited, monitoring sites are usually selected by a "worst case" principle; that is, they are set up where maximum CO concentrations are expected. As a result, many CO sites are located in close proximity to major highways, arterials, and downtown street canyons. This means that they are situated where maximum CO levels occur, but that their scale of representativeness is small. Monitoring results may thus relate primarily to pedestrian exposure near the monitor. Sites located away from the major roadways, but within highly populated neighborhoods with high traffic densities, may be more representative of the maximum CO concentrations to which a large portion of the population of a city may be exposed.

Ott[47] has stated the need for standardization in site selection and has recommended certain siting criteria by station type. Ott's criteria are presented in Table 6-1.

The EPA[84] has also published guidelines for CO monitor siting (Table 6-2). These deviate somewhat from Ott's criteria, primarily in site type definition and recommended separation distance between the station and the nearest major highway. In the EPA's criteria, minimum separation distance is dependent on traffic volume measured in vehicles per day (VPD). In decisions about which sites should be monitored, EPA guidelines[83] give the highest priority to microscale sites within street canyons and to neighborhood sites where maximum concentrations are expected. Table 6-3 lists EPA[83] priorities for various station types.

The variability of CO concentration with height in the vicinity of a highway is sufficiently large that the representativeness of measurements will be strongly affected by variability of the inlet probe height. It is, therefore, necessary to standardize the height of the inlet probe so that data collected at one air monitoring station is comparable to data collected at others. In an effort to characterize typical human exposure, the sample inlet probe height should ideally be at breathing level. However, as a compromise between representation of breathing height and practical considerations, such as prevention of vandalism, it is recommended that inlets for most kinds of sampling be at a height of 3 ± 0.5 m.[1,5] A one-meter minimum separation of the probe from adjacent structures is also recommended to avoid the frictional effects of surfaces on the movement of air.[79]

The number of monitoring sites required depends on the objectives of the monitoring effort and on the complexity of the problem under study. Until May, 1979, EPA guidelines[15] required 1 site for cities with 100,000 or fewer people, 1 plus 0.15 sites per 100,000 people in populations up to 5,000,000, and 6 plus 0.05 sites per 100,000 people in populations greater than 5,000,000.

TABLE 6-1. CRITERIA FOR SITING MONITORING STATIONS[47]

Station Type	Description
TYPE A	Downtown Pedestrian Exposure Station. Locate station in the central business district (CBD) of the urban area on a congested, downtown street surrounded by buildings--a "canyon" type street--and having many pedestrians. Average daily travel (ADT) on the street must exceed 10,000 vehicles/day, with average speeds less than 15 miles/hour. Monitoring probe is to be located 1/2 meter from the curb at a height of 3 ± 1/2 meters.
TYPE B	Downtown Background Exposure Station. Locate station in the central business district (CBD) of the urban area but not close to any major streets. Specifically, no street with average daily travel (ADT) exceeding 500 vehicles/day can be less than 100 meters from the monitoring station. Typical locations are parks, malls, or landscaped areas having no traffic. Probe height is to be 3 ± 1/2 meters above the ground surface.
TYPE C	Residential Population Exposure Station. Locate station in the midst of a residential or suburban area but not in the central business district (CBD). Station must not be less than 100 meters from any street having a traffic volume in excess of 500 vehicles/day. Station probe height must be 3 ± 1/2 meters.
TYPE D	Mesoscale Meteorological Station. Locate station in the urban area at appropriate height to gather meteorological data and air quality data at upper elevations. The purpose of this station is not to monitor human exposure but to gather trend data and meteorological data at various heights. Typical locations are tall buildings and broadcasting towers. The height of the probe, along with the nature of the station location, must be carefully specified along with the data.
TYPE E	Nonurban Background Station. Locate station in a remote non-urban area having no traffic and no industrial activity. The purpose of this station is to monitor for trend analyses, for non-degradation assessments, and for large-scale geographical surveys. The location or height must not be changed during the period over which the trend is examined. The height of the probe must be specified along with the data. A suitable height is 3 ±1/2 meters.
TYPE F	Specialized Source Survey Station. Locate station very near a particular air pollution source under scrutiny. The purpose of the station is to determine the impact on air quality, at specified locations, of a particular emission source of interest. Station probe height should be 3 ± 1/2 meters unless special considerations of the survey require a non-uniform height.

TABLE 6-2. SPECIFIC PROBE EXPOSURE CRITERIA[83]

Site Type	Height Above Ground	Expected Concentration Gradient with Height (1-hr. Average)	Separation of Monitor from Influencing Sources	General Remarks
Street Canyon				
Peak Conc.	3 ± 1/2 m	≅.5 ppm/m	Mid-sidewalk or 2 m from side of building. On leeward side of street.	Central Business District. High density, slow-moving traffic. Dense multiple-story buildings lining both sides of street. >10 m from intersection.
Average Conc.	3 ± 1/2 m	≅.3 ppm/m	Mid-sidewalk or 2 m from side of building.	
Neighborhood			Setback VPD 3.5 km 100,000 1.5 km 50,000 200 m 10,000 100 m 5,000 35 m 1,000 25 m any	Commercial or residential neighborhood. This separation criteria limits the effect of these streets to ≅1 ppm.
Peak Conc.	3 ± 1/2 m	5%/m		
Average Conc.	3 ± 1/2 m	5%/m		
Corridor	3 ± 1/2 m	<.3 ppm/m >5%/m	Dependent on traffic volume, road configuration and setback distance of commercial or residential activity.	Stop and go or limited access traffic >50,000 VPD or greatest in area.

TABLE 6-2 (Continued)

Site Type	Height Above Ground	Expected Concentration Gradient with Height (1-hr. Average)	Separation of Monitor from Influencing Sources	General Remarks
Background	3 to 10 m	.2%/m	5 to 6 km; >3,000 VPH max. 400 m; >100 VPD.	35 km downwind in least frequent wind direction from city, limit effects to .2 ppm.
New Source Review				
Preconstruction	3 ± 1/2 m	5%/m	Usually the same as neighborhood.	Area of lowest concentration in proposed indirect source location for background.
Post-Construction	3 ± 1/2 m	>5%/m to <.5 ppm	Usually the same as corridor or street canyon.	Area of maximum concentration in area of complete area source.

TABLE 6-3. SUGGESTED PRIORITY ORDER FOR CARBON MONOXIDE MONITORING SITES[83]

Site Types	Priority
Peak Street Canyon	#1
Peak Neighborhood	#1
Average Street Canyon	#2
Corridor	#3
Background	#4
Average Neighborhood	#5

Site selection for monitors used for purposes other than trends analysis and determination of compliance with air quality standards may not follow the specific criteria that apply to continuous monitoring sites. In fact, special-purpose studies in which CO concentrations are measured at many locations provide information about the spatial variations of ambient CO that form the basis for setting site-selection criteria. Among the principal types of special-purpose monitoring are research studies for diffusion model development and improvement and for source surveillance studies. Source surveillance studies may be conducted for highways or point sources of CO. Diffusion model development studies may be for line source models (such as HIWAY[76] or CALINE-2[28]) or area source models (such as APRAC-2[36]). For special-purpose studies, criteria for site selection are chosen by the investigator.

UNITED STATES DATA BASE

In accordance with requirements of the Clean Air Act and EPA regulations for State Implementation Plans (SIP's),[15] ambient CO data from state, local, and Federal networks must be reported each calendar quarter to the EPA's Aerometric and Emissions Reporting System (AEROS).[77] As a result, continuous measurements of ambient CO concentrations from numerous cities throughout the United States are available from the U.S. Environmental Protection Agency's National Aerometric Data Bank (NADB) in standard Storage and Retrieval of Aerometric Data (SAROAD) reporting format.[77]

The status of CO monitoring activities nationwide, as reported to the AEROS in 1977, is summarized in Table 6-4. This table lists, by state, the number of CO monitors that recorded any CO data.

The nationwide historical data base for CO is very limited compared with bases for total suspended particulates or sulfur dioxide, but it is expanding. In 1973, 212 sites reported CO data to the EPA.[78] During 1975, 453 sites submitted CO data, though much of it was incomplete.[69] Total numbers of CO monitors reporting during 1976 and 1977 were 448 and 456, respectively.[85] In 1975, 102 sites had three or more years of data, while in 1976 there were 202 sites with at least three years of data.[82] The State of California, with its well established monitoring program, is the major contributor to the national CO data base. California monitors CO at 84 sites.[85]

TABLE 6-4. STATUS OF CO MONITORING IN 1977[85]

	State	Reporting any Data
01	Alabama	4
02	Alaska	6
03	Arizona	16
04	Arkansas	0
05	California	84
06	Colorado	10
07	Connecticut	9
08	Delaware	3
09	District of Columbia	9
10	Florida	12
11	Georgia	4
12	Hawaii	1
13	Idaho	1
14	Illinois	20
15	Indiana	7
16	Iowa	5
17	Kansas	7
18	Kentucky	15
19	Louisiana	0
20	Maine	4
21	Maryland	15
22	Massachusetts	9
23	Michigan	11
24	Minnesota	8
25	Mississippi	0
26	Missouri	14
27	Montana	4
28	Nebraska	3
29	Nevada	3
30	New Hampshire	3
31	New Jersey	22
32	New Mexico	10
33	New York	29
34	North Carolina	1
35	North Dakota	0
36	Ohio	16
37	Oklahoma	4
38	Oregon	5
39	Pennsylvania	13
40	Puerto Rico	0
41	Rhode Island	1
42	South Carolina	3
43	South Dakota	0
44	Tennessee	5
45	Texas	19
46	Utah	6
47	Vermont	2
48	Virginia	15
49	Washington	7
50	West Virginia	2
51	Wisconsin	9
52	Wyoming	0
53	Guam	0
54	Virgin Islands	0
	TOTAL	456

Among the oldest CO monitoring sites are the Continuous Air Monitoring Program stations, which have been operated by the Federal government since 1962.[71] Continuous Air Monitoring Program (CAMP) data have been collected at nine sites, one each in the cities of Los Angeles, San Francisco, Denver, Chicago, New Orleans, St. Louis, Cincinnati, Philadelphia, and Washington, D.C. The stations in Chicago, Cincinnati, Philadelphia, and Washington, D.C., have been part of the program since its inception. The Washington, D.C., station was moved to a new location in 1969, interrupting the continuous data record for that site. The stations in every case are located in the downtown, central business district of the city. *Since a CAMP station consists of only one sampling site per city, its data do not necessarily represent air pollution levels prevailing beyond the immediate vicinity of the station*.

An additional problem with CAMP station data is that continuity is often lacking because of changes in site location or CO monitoring procedures that have been made since the beginning of the program. Specifically, in 1970 the original CO instruments (mono-beam NDIR) were replaced with dual-beam NDIR detectors with integrating chambers added, and in 1971 calibration gases were changed from CO in nitrogen to CO in air. These changes tended to eliminate water vapor interference, smooth out the concentration plots, and eliminate CO_2 interference.[71] Similar changes in CO monitoring procedures were first implemented by the Los Angeles County Pollution Control District in 1968.[61] Figure 6-1 shows the annual mean CO concentrations measured at three Los Angeles Basin sites before and after the changes were made. A significant decrease is apparent in CO levels measured in and after 1968.[61]

Computer retrievals of raw data submitted to the AEROS,[75] and published data summaries such as the *National Air Quality and Emission Trends Report*[71,72,74,78,80,82,85] or *Air Quality Data - Annual Statistics*, are available.[62-69] However, state and local air pollution control agencies are not required to submit all CO data collected from their monitoring network. These agencies may also conduct special studies for certain "in-house" purposes. State departments of transportation and local metropolitan planning commissions are sources of CO data for the preparation of environmental impact statements for proposed transportation projects and/or in the preparation of SIP revisions. Air quality impact research sponsored by the EPA, the Federal Highway Administration, universities, and private industries also are sources of CO data.

TECHNIQUES OF DATA ANALYSIS

Introduction

Air quality surveys inherently involve taking a limited number of samples from a highly variable and uncontrolled population (i.e., the environment). For this reason, air quality data should be analyzed through statistical methods, which can be used to describe the behavior of the total population on the basis of a finite number of samples. In particular, statistical parameters can be calculated to describe the typical values observed, the maximum or peak values observed, and the range of values observed.

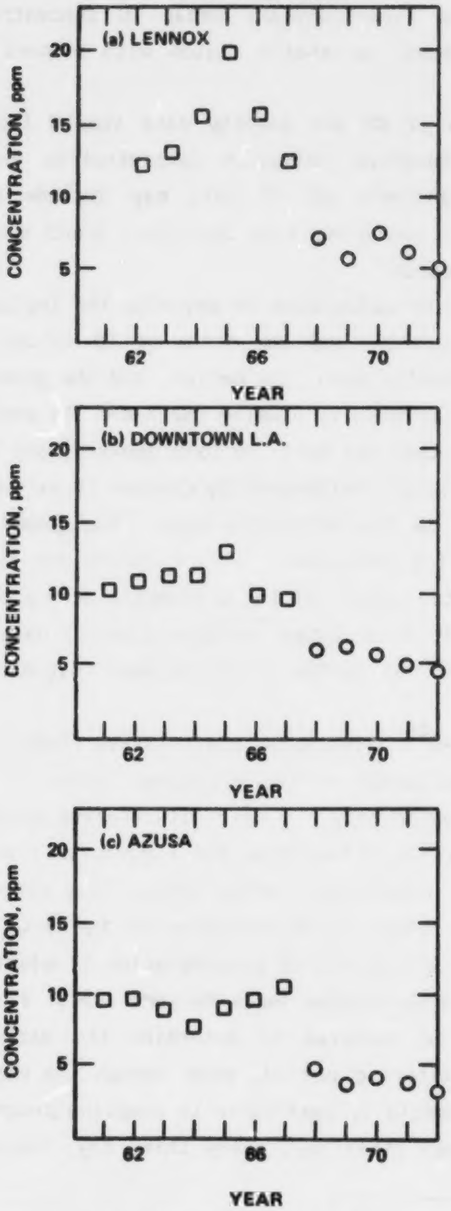

Figure 6-1. Annual average CO levels in Los Angeles.
(Used with permission of Journal of Air Pollution Control Association, 25(II):1129-1136, 1975.)

Although intermittent sampling is an important research tool for conducting special studies, the majority of CO monitoring instruments in use today are intended to operate continuously and to yield successive hourly averages. These data are applied for two principal uses: (1) characterizing environmental conditions by describing short-term (hourly, daily, seasonal) and long-term (year-to-year) urban CO concentration patterns, and (2) evaluating, for statutory purposes, an area's status with respect to the 1-hour and 8-hour average NAAQS for CO.

At a minimum, an analysis of CO air quality data should include a comparison of the highest (or second highest) observed pollution concentration to established air quality standards. In addition, an analysis of CO data may include calculation of population statistics, frequency analyses, averaging time analyses, trend analyses, and case analysis.

Calculation of Population Statistics

Statistical parameters can be calculated to describe the typical CO values observed, the maximum or peak CO values observed, and the range of CO values observed. Indicators of typical CO values are the arithmetic mean, the median, and the geometric mean. When the term "average" is used, the arithmetic mean is usually implied. The median is the middle value of the CO data, that is, the value that has half the data above it and half below it. The median is a convenient statistic that is not influenced by changes in extremely high or low CO values of the distribution, as would be the arithmetic mean. The geometric mean* is probably the least intuitive of the statistics presented. If a distribution is symmetrical, such as the normal distribution, the expected values of the arithmetic mean and of the median are identical. However, for a lognormally distributed variable (and CO data often have a distribution that is approximately lognormal), it is the geometric mean that more closely approximates the median.

The histogram of Figure 6-2[45] illustrates the relative frequency of occurrence of 1-hour average CO concentrations. The shape of the histogram, which is "skewed to the right," is typical for lognormally distributed data. A more illustrative method of plotting the data is shown in Figure 6-3.[45] This curve illustrates the cumulative frequency distribution of the data when they are plotted on logarithmic versus probability (log-probability) graph paper. In plottings of the cumulative frequency distribution of the data, each point represents the cumulative frequency with which a specific CO concentration is equaled or exceeded.

The cumulative frequency distribution leads to some useful statistical applications that allow CO monitoring data to be analyzed to determine the maximum CO concentration that probably occurred during a monitoring period, even though the maximum value itself may not have been recorded. This is especially applicable to sampling programs designed to collect CO data intermittently (i.e., every other day, every third day, randomly selected days, etc.).

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*-The geometric mean is calculated by taking the logarithm of each sampled concentration, adding all of them together, dividing by the number of samples, and taking the antilog.

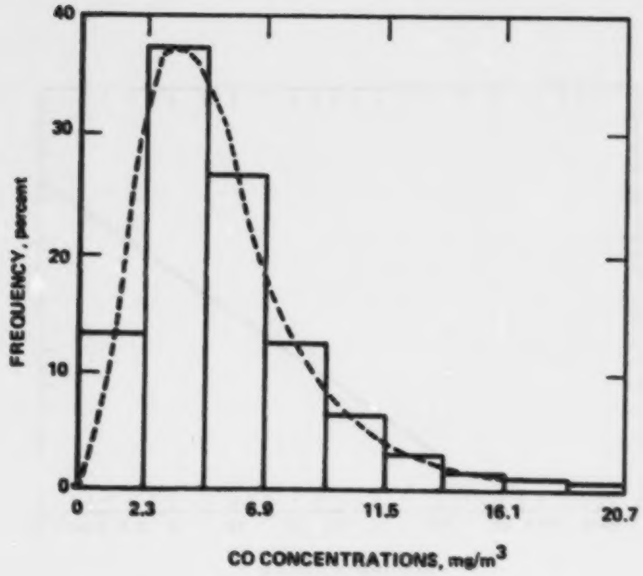

Figure 6-2. Histogram of 1-hr average CO concentrations, Washington, DC (CAMP).[46]

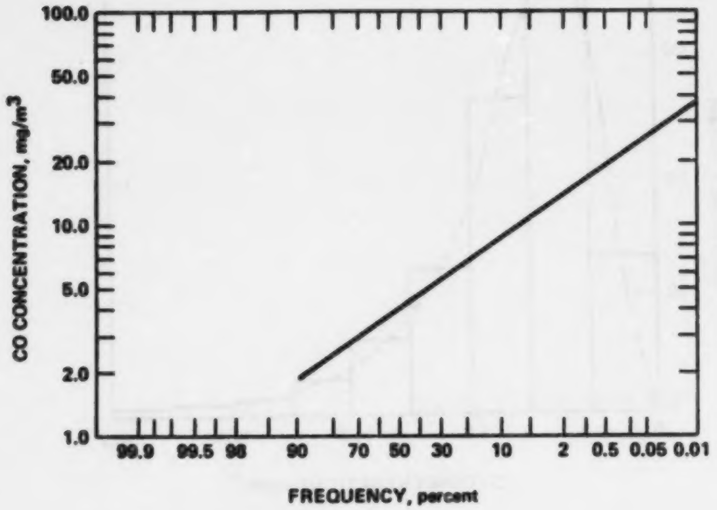

Figure 6-3. Cumulative frequency distribution of 1-hour average CO concentrations.

It also applies to continuous CO monitoring where data are missed because of calibrations, maintenance, or instrument failure. The assumption of data lognormality allows these "missed" values to be estimated. The actual days on which maximum CO concentrations occurred cannot be determined, but the frequency of occurrence of high CO concentrations can.

Maximum CO values may be indicated by listing the maximum and/or the second highest value. The second highest value is important because compliance with the short-term air quality standards for CO is determined by this value. Since the second highest value does not allow for differences in sample sizes, difficulty would arise if continuous CO monitoring data were missed because of calibrations, maintenance, or instrument failure; or if CO were sampled intermittently. To allow for dependence on sample size, percentiles are sometimes used to indicate maxima. Use of a percentile value, rather than an absolute count of samples, allows for sampling schedules that differ from site to site and year to year.

The statistics customarily used to indicate the variability of CO data are the arithmetic standard deviation and the geometric standard deviation. Ranges or percentiles can also be used as indicators of spread. These statistics provide a measure of the uniformity of the data.

Frequency Analysis

A number of investigators,[1,31-33,49,91] primarily Larsen and Zimmer,[33] have shown that short time-averaged air pollution concentrations (from 5-minute to 24-hour averages) sampled over a much longer period of time (i.e., weeks, months, or years) tend to be lognormally distributed within the longer sampling interval. Described simply, a lognormal frequency distribution means that CO data collected frequently exhibit many low concentrations, a significant number of moderate concentrations, and a relatively small number of extreme, peak, or maximum concentrations.

While the standard lognormal model is commonly used in evaluating air pollution data, other investigators continue to search for improved methods of statistically describing concentration distribution. Examples of these are the three-parameter lognormal distribution, proposed by Mage and Ott,[37] and the Weibull and Gamma distributions studied by Pollack.[49]

Comparison of CO Data to National Ambient Air Quality Standards

The NAAQSs for CO are currently based on a 1-hour and an 8-hour averaging time. Carbon monoxide data are most frequently collected in time averages of 1 hour. Evaluating compliance with the 1-hour standard simply requires rank-ordering 1-hour values for a year and comparing the second-highest value with the 1-hour standard, which is currently 40 mg/m^3 (35 ppm), not to be exceeded more than once per year. If the second-highest 1-hour value is less than 40 mg/m^3, the standard has been met.

Evaluating compliance with the 8-hour standard involves the calculation of moving 8-hour averages from the 1-hour data set. These 8-hour averages are also rank-ordered to obtain the second-highest non-overlapping value for comparison with the 8-hour standard, which is currently 10 mg/m^3 (9 ppm). For enforcement purposes, only non-overlapping 8-hour intervals are counted as violations, as discussed in the Guidelines for the Interpretation of Air Quality Standards.[92] It has been shown, however, that the full set of moving 8-hour averages should be examined for excessive values. Proposed simplifications, such as calculating only three consecutive non-overlapping 8-hour averages per day, can easily result in missing peak 8-hour intervals and may not afford equitable comparisons among stations with differing diurnal patterns.

For partial data sets, if continuous CO monitoring data were missed because of calibrations, maintenance, or instrument failure, or if CO were sampled intermittently, comparison of the CO data to standards by means of lognormal cumulative frequency distribution plots may be useful. Once the CO data have been plotted on log-probability graph paper, the frequency of equaling or exceeding any specified CO concentration can easily be determined. For example, in Figure 6-3, observe that the CO concentration equals or exceeds 10 mg/m^3 for 7 percent of the time and 20 mg/m^3 for 0.05 percent of the time. The NAAQS for a 1-hour average concentration may not be exceeded more than once per year. The frequency of occurrence of the second highest concentration can be expressed as a percentage by dividing 2 hours by the number of hours in a year (i.e., $2 \div 8{,}760 = 0.02284$ percent).

Averaging Time Analysis

A method that can be used to determine a maximum 8-hour average CO concentration when only 1-hour average data are available is a mathematical model developed by Larsen[32] and known as "Larsen's Transform." Data fitting this model can be graphed as shown in Figure 6-4, which includes the maximum, minimum, and frequency of equaling or exceeding specified CO concentrations for averaging times ranging from one second to one year. The most useful and important part of the graph, however, is the annual maximum line, which can be used to determine the annual maximum 8-hour average CO concentration from 1-hour average values.

Trend Analyses

Carbon monoxide concentrations vary considerably from hour to hour, day to day, season to season, and year to year. These variations are usually not random but follow fairly predictable temporal patterns according to season of the year, day of the week, and hour of the day. Predicted, long-term, statistical variations in CO concentrations are referred to as trends.

Carbon monoxide trends are best illustrated by graphs that can show diurnal, daily, seasonal, or yearly CO concentration comparisons. Examples of the different ways trends can be shown are provided later in this section.

Carbon monoxide concentrations also follow fairly predictable spatial patterns. Spatial distributions of CO concentrations can be illustrated by the use of isopleth maps. Isopleth CO concentration maps can be prepared that illustrate the spatial distribution of average CO concentrations, maximum CO concentrations, typical CO values during a particular time of day or season of year, or the CO concentration distribution that typically occurs under specific meteorological conditions (wind speed, wind direction, atmospheric stability). Isopleth maps are especially useful for illustrating the size of the geographical area affected by CO levels. Sample isopleth maps are shown in Figures 6-5[17] and 6-6.[60]

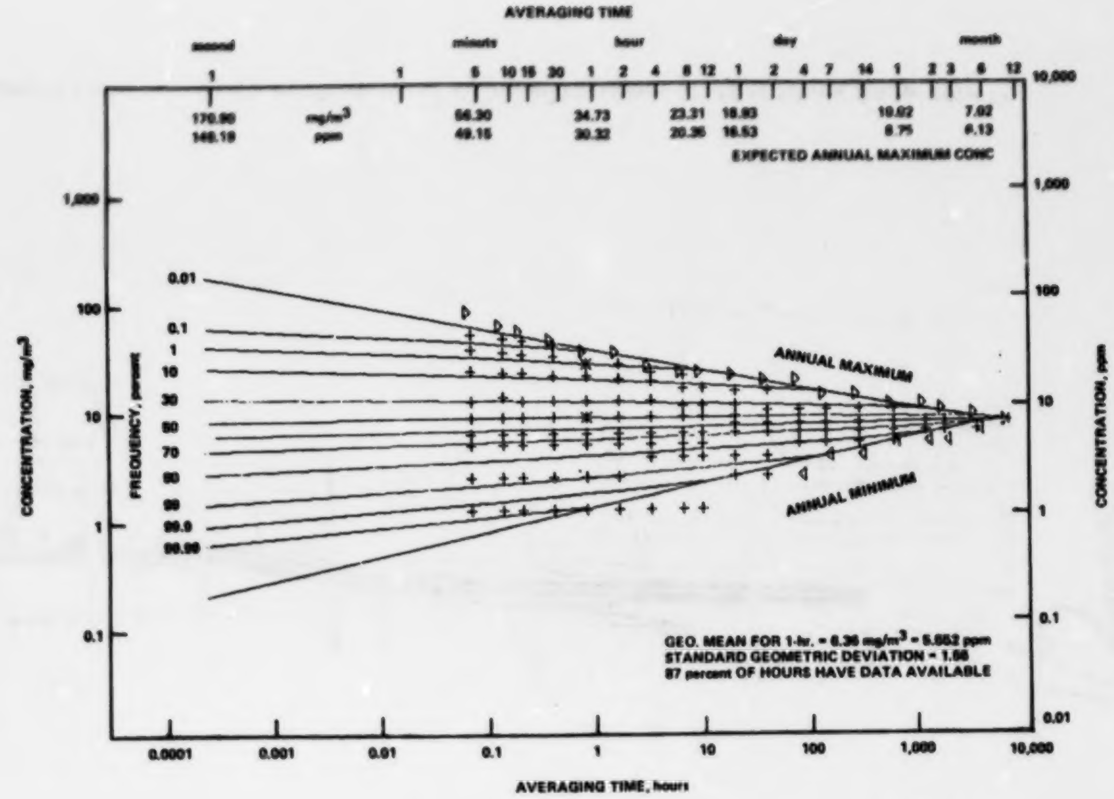

Figure 6-4. Concentration vs. averaging time and frequency for carbon monoxide from 12/1/63 to 12/1/68 at site 662, St. Louis.

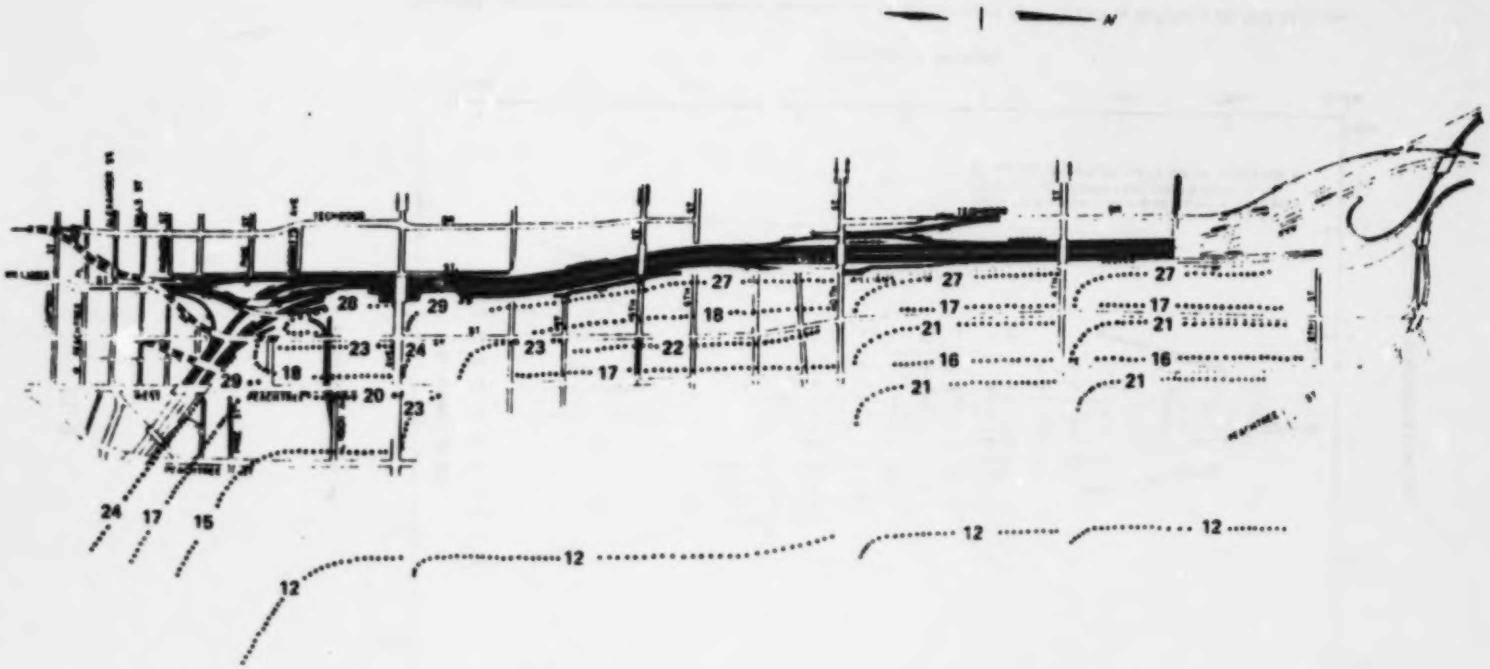
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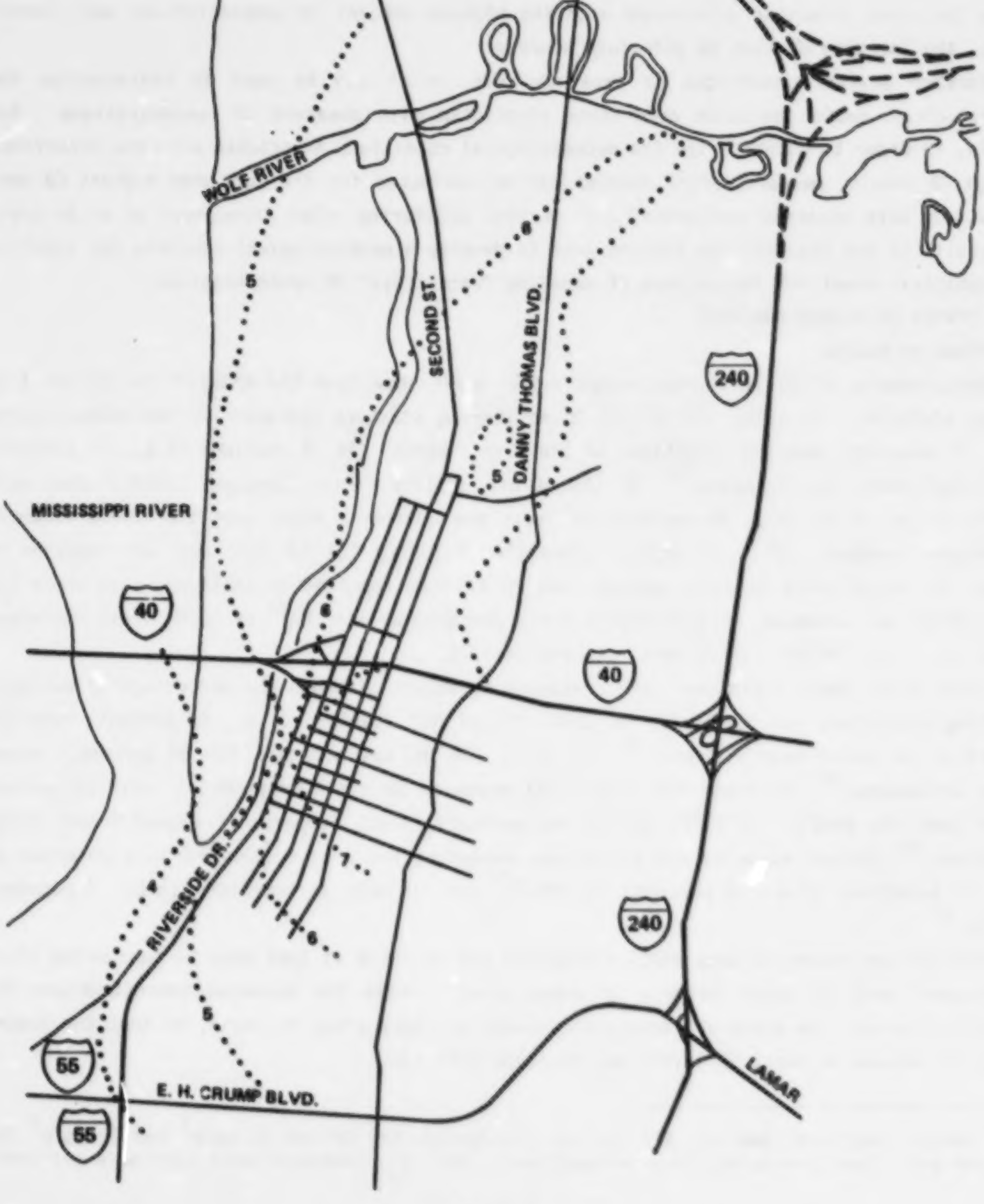
Figure 6-5. Predicted 1-hour average ambient CO concentrations (mg/m^3) in vicinity of I-85 in Atlanta, GA, for 1976.[18]


E. A. 101
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DANNY THOMAS BLVD.
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MISSISSIPPI RIVER
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RIVERSIDE DR.
7
6
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5
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E. H. CRUMP BLVD.
LAMAR
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Figure 6-6. Measured 8-hour average background CO concentrations in Memphis, TN.[62]

Special Analyses

A useful analysis technique not previously presented is the "pollution rose," as illustrated in Figure 6-7. The pollution rose presents the joint frequency distribution of wind direction versus ambient CO concentration. The pollution rose is very helpful in determining the wind direction associated with the highest ambient CO concentrations and, intuitively, the location of high CO emissions sources.

Another analysis technique is case analysis, which can be used to characterize the meteorological and/or emission conditions associated with observed CO concentrations. For example, in order to characterize the meteorological conditions associated with the occurrence of high CO levels, meteorological records can be evaluated for the days when highest CO concentrations were observed concurrently at several monitoring sites throughout an urban area. The results of the analysis can then be used to develop a meteorological scenario for input to a mathematical model for the purpose of modeling "worst-case" CO concentrations.

URBAN LEVELS OF CARBON MONOXIDE

Comparison to NAAQSs

Measurements of CO in United States urban areas show that the NAAQSs* for CO are frequently violated. In 1973, 153 of 212 CO monitoring stations operated in the United States (i.e., 72 percent) reported violations of the 8-hour NAAQS. At 24 stations (i.e., 11 percent) the 1-hour NAAQS was exceeded.[74] Of the 30 Air Quality Control Regions (AQCRs) that were Priority I for CO in 1973, 26 reported at least one quarter's data, and 25 of these exceeded the 8-hour standard. Also, 34 AQCRs, classified Priority III in 1973 and not required to monitor CO, established monitors anyway, and 28 of them reported at least one site where the 8-hour NAAQS was exceeded. Figure 6-8 is a map prepared by the EPA[74] of AQCRs locations where violations of the NAAQSs for CO were recorded in 1973.

Since 1973, NAAQS violations have continued to occur, although the percentage of monitors reporting violations has decreased. In 1974, 211 of 377 stations (i.e., 56 percent) reported violations of the 8-hour standard.[78] In 1975, 234 of 434 monitors (or 54 percent) showed 8-hour violations.[80] Of these 234 sites, 111 measured CO concentrations at least 50 percent higher than the NAAQS. In 1977, 211 of 456 monitors (i.e., 46 percent) showed 8-hour NAAQS violations.[85] Carbon monoxide concentrations exceeding the 1-hour standard were observed at only 27 locations (i.e., 6 percent) in 1975[80] and at only 11 locations (i.e., 2 percent) in 1977.[85]

Part of the reason so many NAAQS violations are observed is that most CO monitoring sites are located next to major streets in urban areas. While the measured concentrations are probably accurate, the scale of representativeness of these sites is small, so that the number of people exposed to these CO levels may be relatively low.

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*-The NAAQSs (National Ambient Air Quality Standards) for CO are 10 mg/m^3 and 40 mg/m^3 for 8-hour and 1-hour averaging times, respectively, not to be exceeded more than once per year.

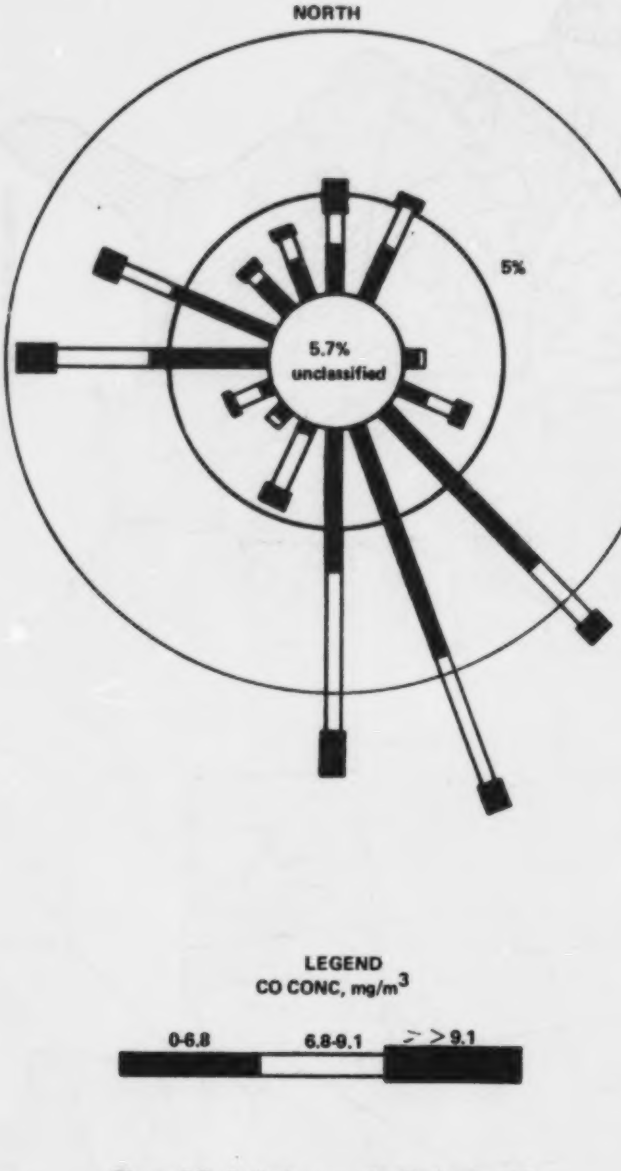

Figure 6-7. Pollution rose for St. Louis, MO.

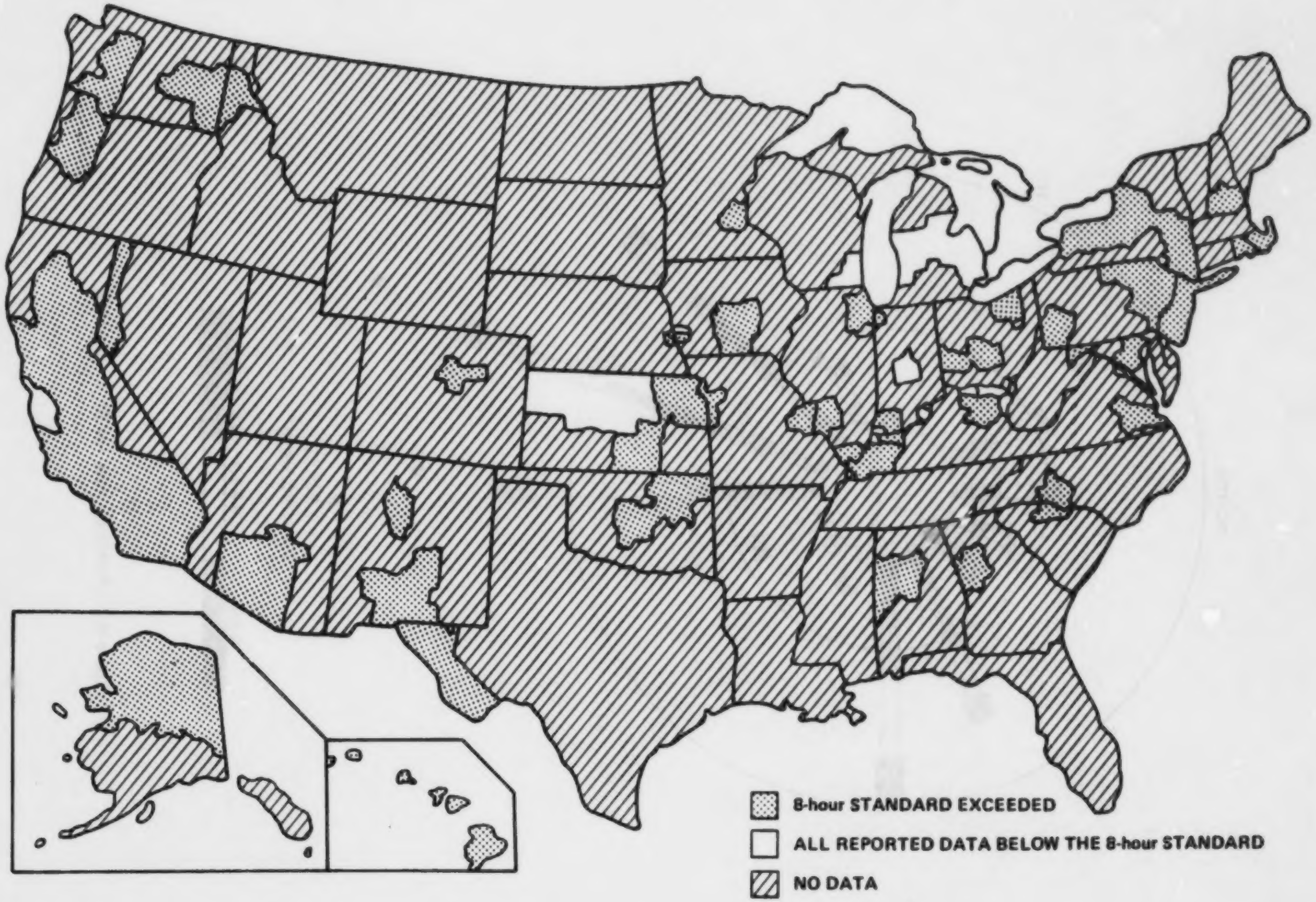
▩ 8-hour STANDARD EXCEEDED
☐ ALL REPORTED DATA BELOW THE 8-hour STANDARD
▨ NO DATA

Figure 6-8. Status of carbon monoxide levels, 1973.[70]

Hourly Patterns

Ambient CO concentrations may follow regular hourly patterns of variation that result from nearby vehicular traffic and meteorological factors affecting dispersion of the CO. The three examples shown in Figures 6-9, 6-10, and 6-11 illustrate the annual average and "worst case day" hourly CO curves based on 1977 data from CO monitoring sites in Baltimore, Maryland,[41] Denver, Colorado,[10] and Los Angeles, California,[57] respectively. (The "worst case day" is defined herein as that day on which the annual maximum 8-hour average CO concentration was observed.) While the exact shape and magnitude of the hourly CO curve for these communities is dependent to a large extent on meteorological factors, two peaks corresponding with the morning and evening "rush hour" traffic are evident in the figures. For comparison, an example of typical hourly variations in traffic volume is given in Figure 6-12.[86] A third peak in CO concentration during the late evening/early morning hours can also be noted in several of the figures. This peak is influenced by late night calm meteorological conditions.

Carbon monoxide levels in most of the cities generally reach their initial daily maximum between 7:00 and 9:00 a.m., coincident with heavy morning automobile traffic and prior to inversion layer breakup. The second peak is usually reached in the late afternoon between 4:00 and 7:00 p.m. The late evening peak generally occurs between 10:00 p.m. and 12:00 midnight. Although the morning peak in CO concentrations is generally the highest, Figure 6-10 illustrates that the opposite can also occur.

Seasonal Patterns

Ambient CO levels also follow seasonal patterns. Figures 6-13, 6-14, and 6-15 show the seasonal arithmetic mean, maximum 8-hour and maximum 1-hour CO concentrations based on 1977 data for Baltimore,[41] Denver,[10] and Los Angeles,[57] respectively. These figures show the highest ambient CO concentrations during the winter.

In the winter, the tendency toward colder ambient temperatures results in increased production of CO emissions from cars, as well as CO added by other fuel burning sources. Also, the more stable atmospheric conditions and low wind speeds of winter result in decreased dispersion of CO emissions and contribute substantially to the occurrence of high ground level CO concentrations.

Annual Patterns

Annual trends in CO concentrations are presented in Figures 6-16 through 6-23 for Baltimore,[40] Denver,[10,11,62] Los Angeles,[56,57,62] Chicago,[74] Cincinnati,[74] Philadelphia,[74] St. Louis,[74] and Washington, D.C.[74] Plotted are the highest 1-hour average, the highest 8-hour average, and the annual arithmetic mean concentration observed each year.

For Baltimore County, monitoring data from 1976 show a factor of 3.4 decrease in annual maximum 1-hour average CO concentrations and a similar decrease (i.e., a factor of 3.1) in annual maximum 8-hour average CO concentrations compared with 1967 levels.

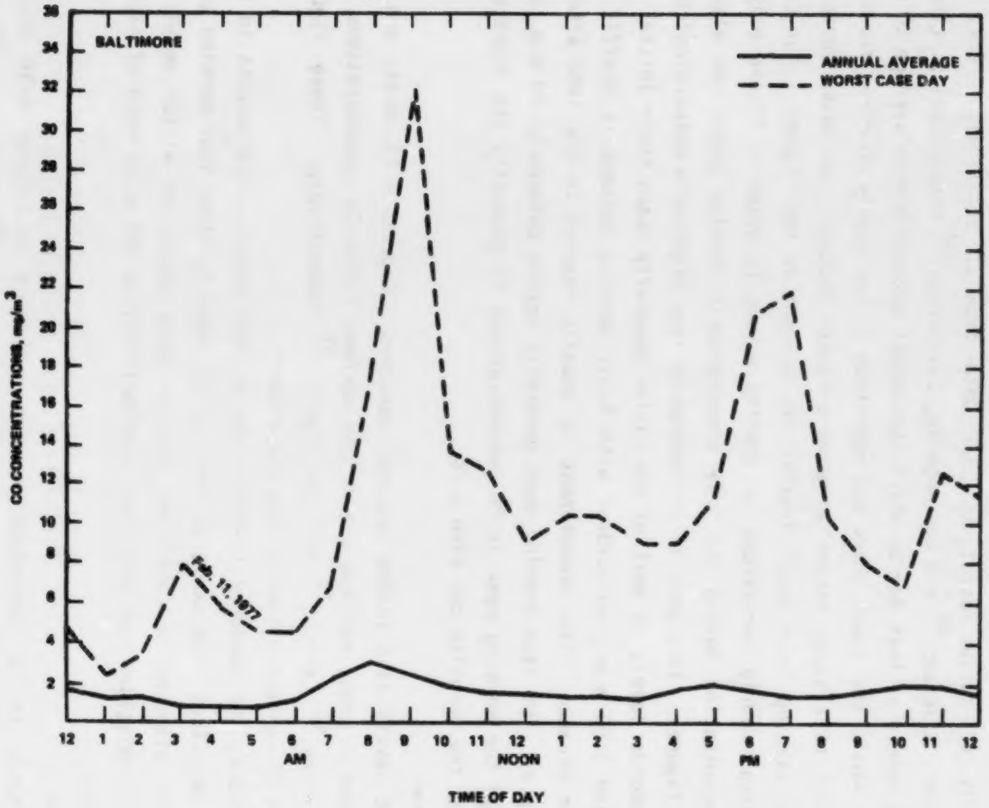

Figure 6-9. Hourly variations of ambient CO concentrations for Baltimore, MD.[42]

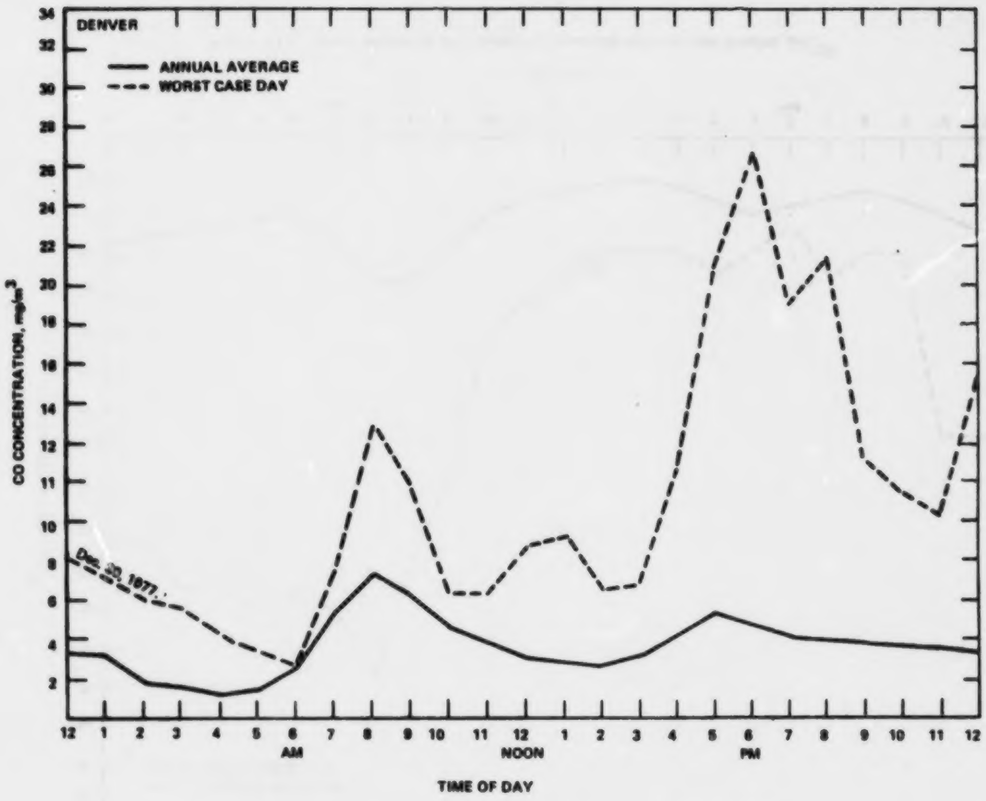

Figure 6-10. Hourly variations of ambient CO concentrations for Denver, CO.[10]

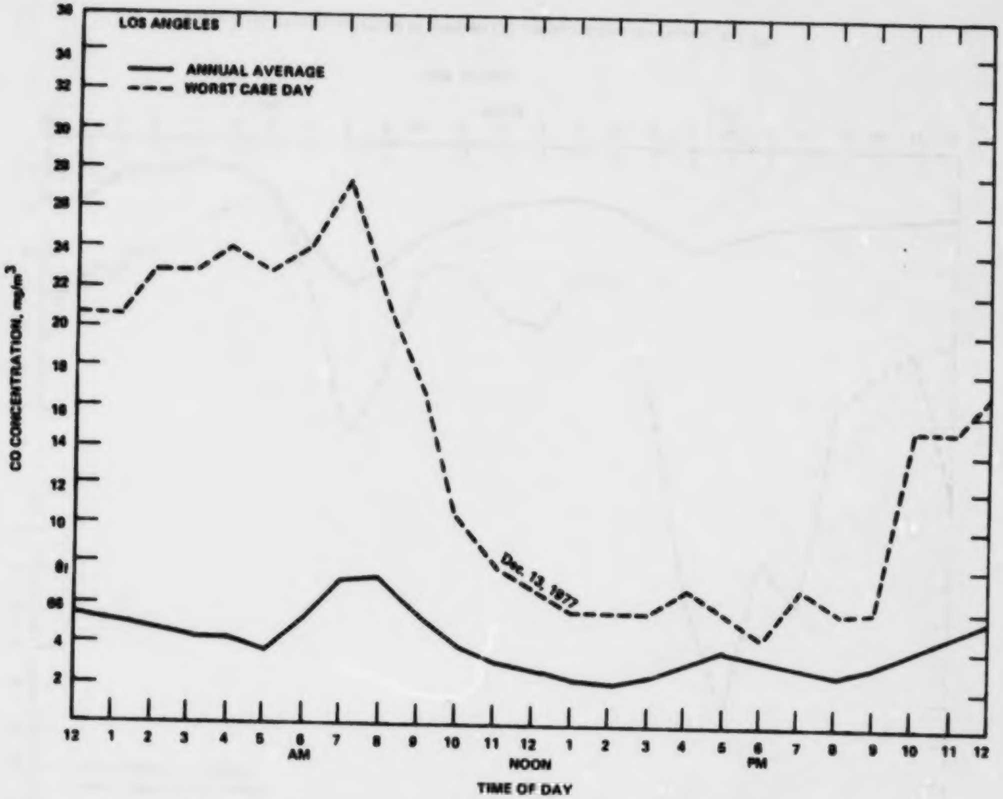

Figure 6-11. Hourly variations of ambient CO concentrations for Los Angeles, CA.[58]

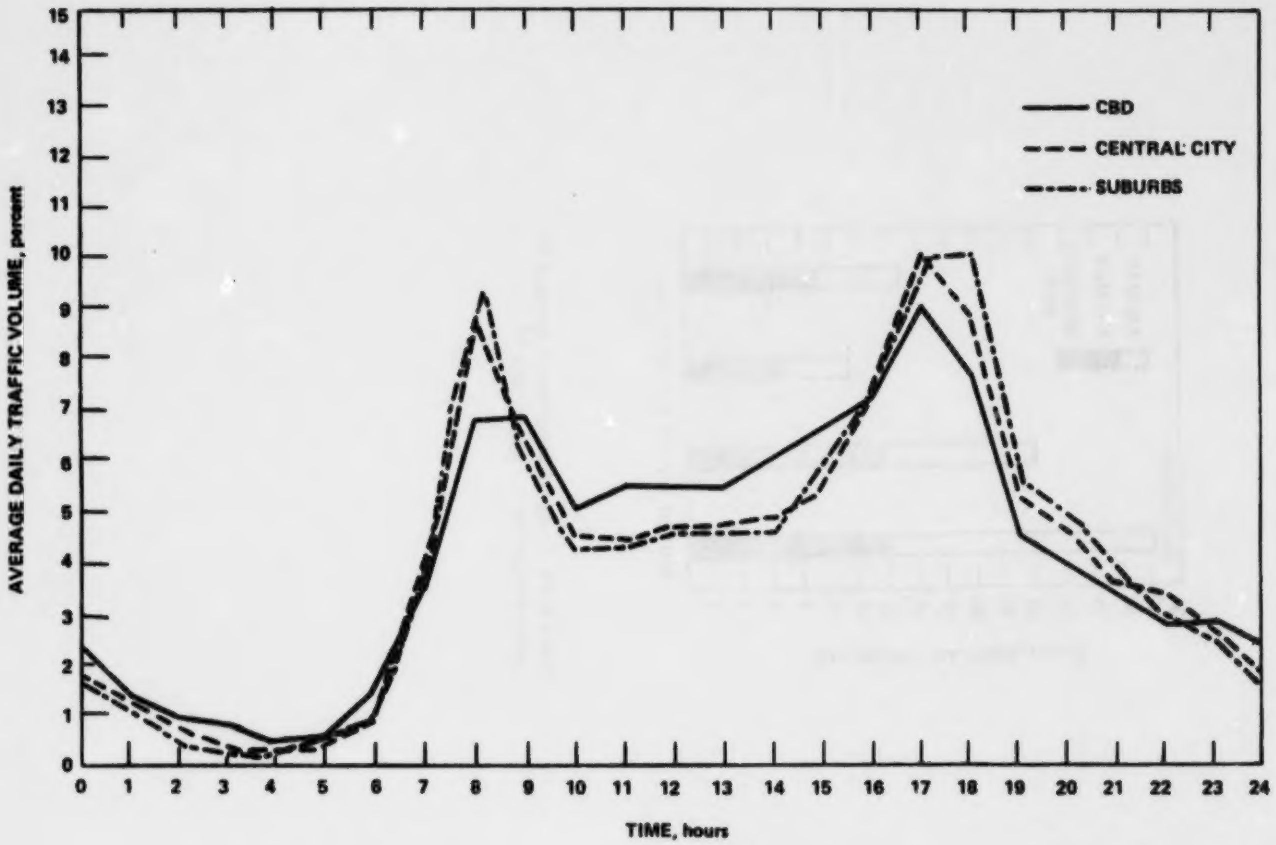

Figure 6-12. Hourly variations of traffic volume.[82]

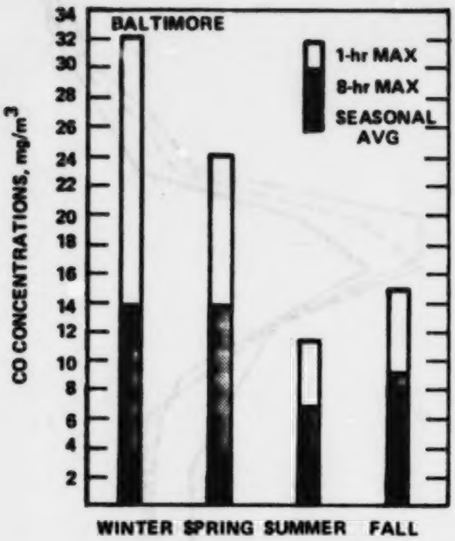

Figure 6-13. Seasonal variations of ambient CO concentrations for Baltimore, MD.[42]

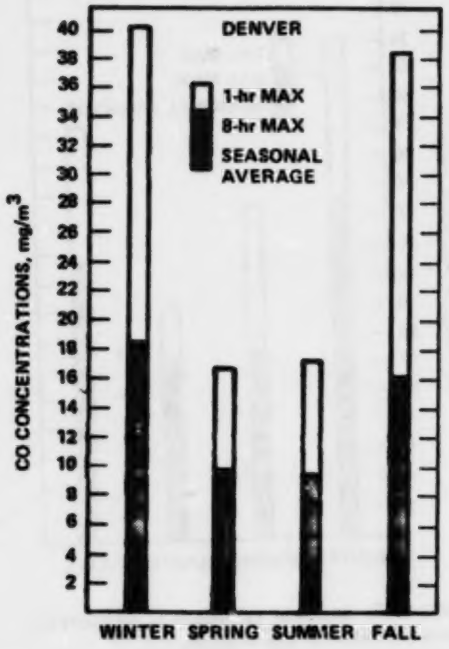

Figure 6-14. Seasonal variations of ambient CO concentrations for Denver, CO.[10]

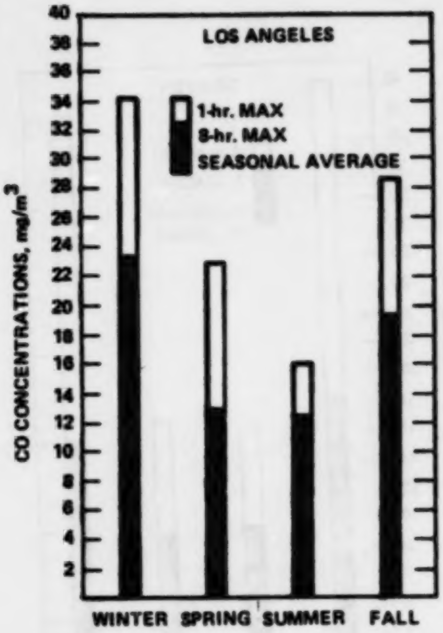

Figure 6-15. Seasonal variations of ambient CO concentrations for Los Angeles, CA.[58]

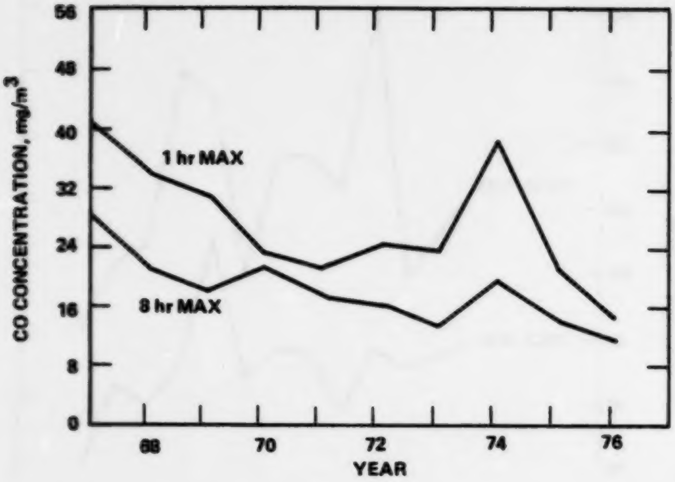

Figure 6-16. Annual variations of ambient CO concentrations for Baltimore, MD.

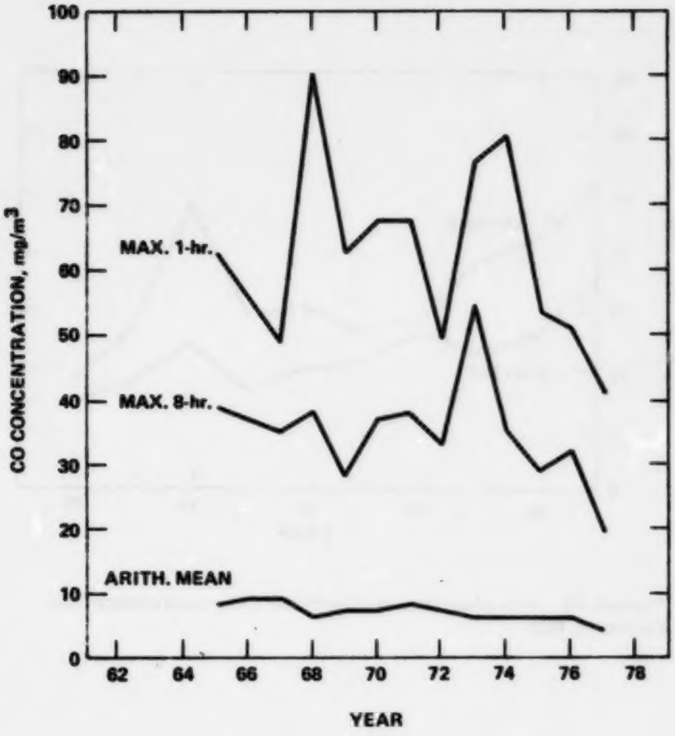

Figure 6-17. Annual variations of ambient CO concentrations for Denver, CO.

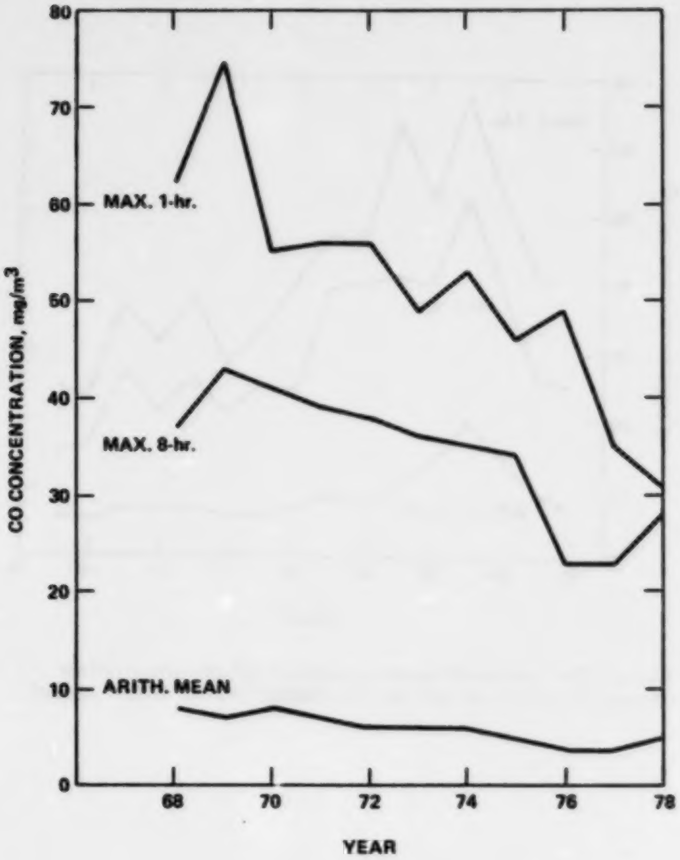

Figure 6-18. Annual variations of ambient CO concentrations for Los Angeles, CA, SAROAD Site No. 053900001.

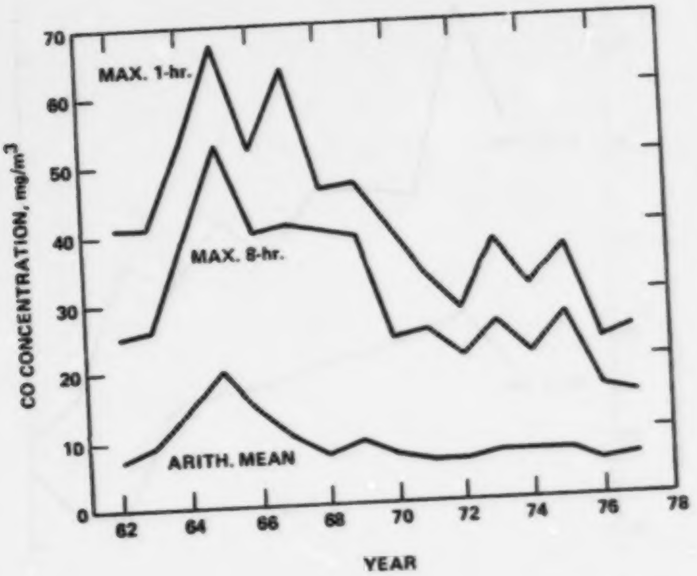

Figure 6-19. Annual variations of ambient CO concentration for Chicago, IL, SAROAD Site No. 141220002 (former CAMP station).

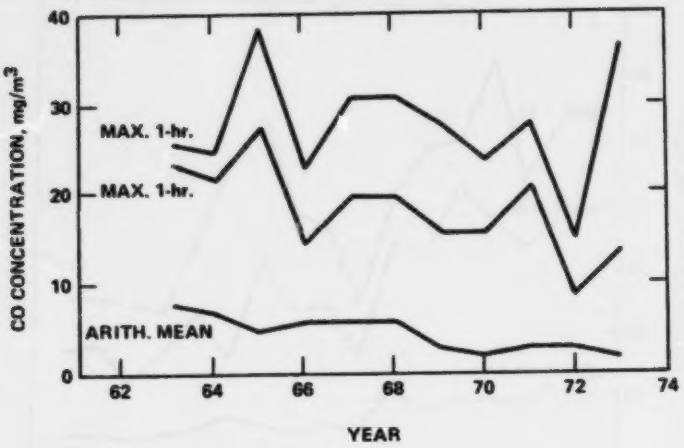

Figure 6-20. Annual variations of ambient CO concentrations for Cincinnati, OH, SAROAD Site No. 361220003 (former CAMP station discontinued in 1973).

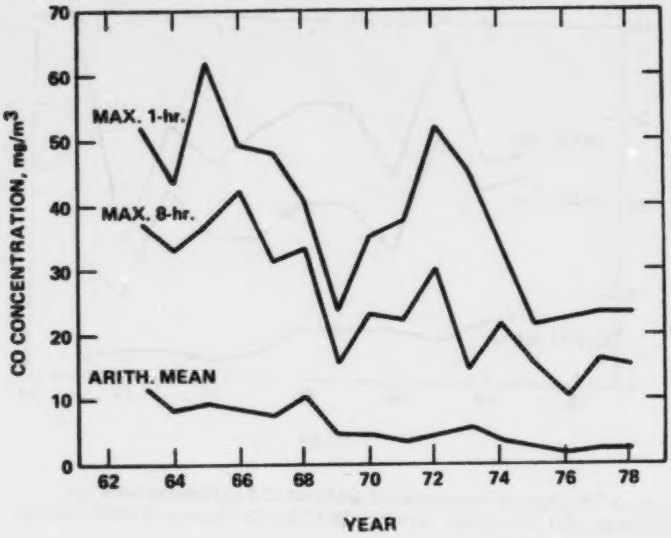

Figure 6-21. Annual variations of ambient CO concentrations for Philadelphia, PA, SAROAD Site No. 397140002 (former CAMP station).

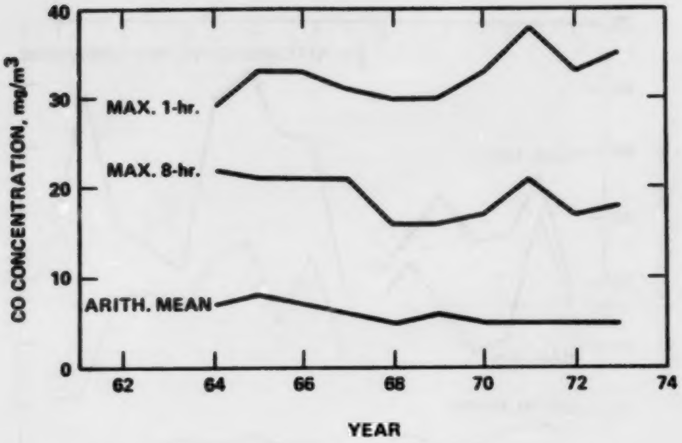

Figure 6-22. Annual variations of ambient CO concentrations for St. Louis, MO, SAROAD Site No. 264280002 (former CAMP station discontinued in 1973).

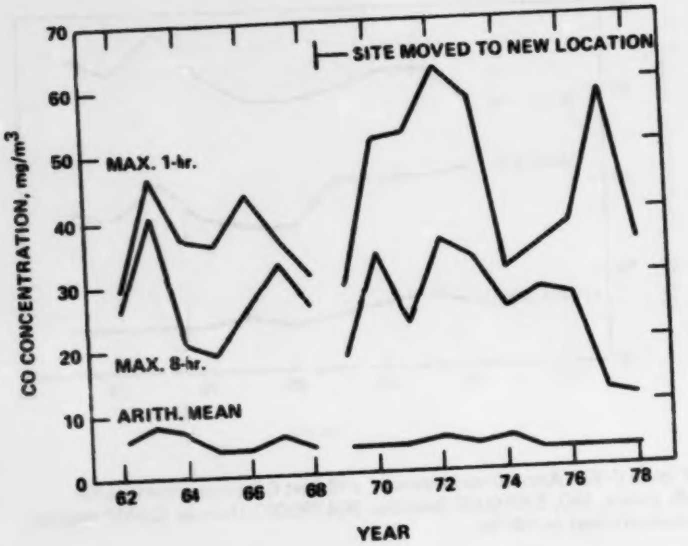

Figure 6-23. Annual variations of ambient CO concentrations for Washington, DC, SAROAD Site No. 090020002 moved in 1969 and redesignated No. 090020003 (former CAMP station).

For Denver, a 53 percent and 32 percent decrease in annual maximum 1-hour and 8-hour average CO concentrations, respectively, has been observed from 1968 to 1977. The annual arithmetic mean CO concentration has decreased 44 percent from 1968 to 1977. The number of observed NAAQS violations has also decreased in Denver over a 10-year period. Eighty-three violations of the 8-hour standard were observed in 1968. This peaked to 153 observed violations in 1972, then decreased to 48 in 1977. The number of violations of the 1-hour standard has decreased from six observations in 1968 to one observation in 1977.

For Los Angeles, a 50 percent and 24 percent decrease in annual maximum 1-hour and 8-hour average concentrations, respectively, has been observed from 1968 to 1978. A 45 percent decrease in the annual arithmetic mean CO concentration has been observed from 1968 to 1978. Although a significant reduction in ambient CO concentrations has been observed in Los Angeles, the number of observed NAAQS violations still remains relatively high. Sixty-four violations of the 8-hour standard were observed in 1977, compared with 172 observed violations in 1968.

A general trend of decreasing ambient CO levels is evident in most of the curves presented. This trend toward lower ambient CO concentrations is presumably due to the lower CO emissions of later model automobiles that have incorporated air pollution controls.

Air monitoring results have been presented only from selected sites in several major U.S. cities. These sites are generally close to major highways and thus measure some of the highest CO concentrations; however, measurements at the sites are not necessarily representative of CO concentrations in these cities. Monitoring sites in the same cities but located 100 to 200 meters from any highway would be expected to record much lower concentrations. More information on CO levels measured in U.S. cities is published annually in the EPA's Air Quality Trends Reports.[71,72,74,78,80,82,85]

SPECIAL CARBON MONOXIDE EXPOSURE SITUATIONS

There are a number of circumstances under which people may be exposed to unusually high concentrations of CO. Some of these result from the operation of automobiles in poorly ventilated areas such as highway tunnels, urban street canyons, and underground parking garages. Other high CO exposure situations may occur where auto emissions are unusually high because of large traffic volumes and congested conditions such as those near large arterial intersections, freeway toll booths, shopping centers, sports stadiums, and roadway repair and construction sites. Commuters may also be exposed to high CO concentrations either within their cars (especially if they are smoking) or from the ambient air. Exposure to CO emitted by cars on city streets is of special concern for bicyclists.

Some occupations require working on or very close to automobile traffic for long periods of time during the work day. People who are on street repair crews or are street cleaners, vendors, delivery men, toll collectors, garage attendants, police, or taxi or bus drivers may be exposed to unusually high concentrations. There are other occupations in which exposure to

CO is due to sources other than automobiles. These include fire fighters, certain airport workers, and some miners and foundry workers.

Variations with Type of Vehicle Traffic

Ambient CO concentrations near city streets were reported as high as 57 mg/m^3 (49.6 ppm) for the 1-hour average and 41.4 mg/m^3 (36.0 ppm) for the 8-hour average for the "worst case" New York City site in 1975. Similar measurements in Los Angeles showed CO concentrations of 60 mg/m^3 (52.2 ppm) for the 1-hour average and 49.7 mg/m^3 (42.6 ppm) for the 8-hour average.[42] These measurements represent some of the highest ambient concentrations of CO reported in the United States near open city streets.

Concentrations of CO in highway tunnels have been reported by several investigators. Ayres et al.[4] have reported 30-day average CO concentrations of 72.5 mg/m^3 (63 ppm) measured at the Queens Midtown Tunnel in New York and a 1-hour maximum of 250 mg/m^3 (217 ppm). Measurements at the Sumner Tunnel in Boston showed 1-hour average CO concentrations as high as 145.2 mg/m^3 (126.3 ppm), with a 24-hour maximum of 58.4 mg/m^3 (50.8 ppm).[44] Miranda et al.[44] reported that many tunnels usually operate below 115 mg/m^3 (100 ppm) CO, employing emergency ventilating fans whenever CO levels exceed 287.5 mg/m^3 (250 ppm).

Wright et al.[88] measured CO concentrations in underground parking garages. They found CO levels in excess of 115 mg/m^3 (100 ppm) in enclosed, unventilated garages. Similar measurements taken in a well-ventilated underground parking facility showed maximum CO concentrations of 49.5 mg/m^3 (43 ppm).

In a study conducted by Patterson et al.,[48] CO measurements were made in the vicinity of Liberty Tree Mall, a regional shopping center in the Boston area. The study was conducted for 2 weeks prior to Christmas of 1973. The maximum 1-hour average concentration measured was 35.2 mg/m^3 (30.6 ppm), and the maximum 8-hour average was 16.3 mg/m^3 (14.2 ppm).

A similar study was conducted by Bach et al.[5] at two sports arenas: Three Rivers Stadium in Pittsburgh, Pennsylvania, and Atlanta Stadium in Atlanta, Georgia. Measurements were made during both day and night baseball games in June and July, 1973. The maximum 1-hour average CO concentration measured was 28.8 mg/m^3 (25 ppm); the 8-hour maximum was 9.4 mg/m^3 (8.2 ppm).

In order to determine the CO exposure to bicyclists, Kleiner and Spengler[29] conducted a study in Boston during the summer of 1974. As expected, CO exposures for bicyclists on city streets were a function of traffic volume, street configuration, proximity of traffic, and ventilation. Typical summer exposures were between 12.7 and 17.3 mg/m^3 (11 and 15 ppm) for trips ranging from 10 to 45 minutes. In no case did the trip-averaged exposure approach the 1-hour NAAQS standard of 40 mg/m^3 (35 ppm).

Car Passenger Exposure to Carbon Monoxide

Carbon monoxide concentrations have also been measured inside automobiles. Chaney[8] measured CO concentrations within an automobile traveling on the Dan Ryan Expressway (I-94) in Chicago, and on the San Diego Freeway (I-405) in Los Angeles and found that CO levels varied with traffic speed. According to Chaney, "when the traffic slowed to 10 mph (16 kph) the CO concentration usually exceeded 17.3 mg/m^3 (15 ppm); when it halted completely, the CO concentration was about 51.8 mg/m^3 (45 ppm)." Chaney also observed that pollution concentration varied inside his automobile with the type and age of vehicle he was following. Heavily-loaded vehicles produced the highest results. While following a truck over the Sierra Nevada mountains, Chaney recorded CO concentrations reaching 57.5 mg/m^3 (50 ppm) on the steepest grade and remaining over 28.8 mg/m^3 (25 ppm) for 30 minutes. Wright et al.[88] have reported CO concentrations of 104 mg/m^3 (90 ppm) inside an automobile due primarily to CO from passengers' cigarette smoke.

Occupational Exposure

Certain occupations inherently involve exposure to CO. Xintaras et al.[89] have reported CO exposures of six toll collectors working on I-65 in Louisville, Kentucky. The maximum 8-hour average concentration measured at the immediate work area was 65.6 mg/m^3 (57 ppm). Over the 12 days of the study, the average 8-hour exposure was 26.2 mg/m^3 (22.8 ppm).

Measurements of CO concentrations in foundry air have been made by Virtamo and Tossavainen.[87] They found that iron cupola exhaust gases may contain 20 to 30 percent CO. Forty-six measurements of CO concentration in the vicinity of the cupolas showed an average of 276 mg/m^3 (240 ppm). They also measured an average 127 mg/m^3 (110 ppm) CO in the casting area of foundries (909 samples) and 97.8 mg/m^3 (85 ppm) in the breathing zone (61 samples) of foundry workers. Similar measurements in steel foundries showed less than 23 mg/m^3 (20 ppm) of CO in areas around electric furnaces. Measurements in the melting and casting areas of copper alloy foundries averaged 23 mg/m^3 (20 ppm) of CO.

Rodgers[53] measured CO concentrations resulting from the use of explosives in phosphate and copper mine environments. Carbon monoxide concentrations exceeded 173 mg/m^3 (150 ppm) for 45 minutes and exceeded 58 mg/m^3 (50 ppm) for 110 minutes during shot firing of nitroglycerin explosives within the mine. Ammonium-nitrate-oil and water gel type explosives tended to produce less CO than did equal weights of nitroglycerin explosives.

Fire fighters can be exposed to very high concentrations of CO by smoke inhalation. Loke et al.[34] and Radford and Levine[50] both report maximum carboxyhemoglobin (COHb) levels of 10 to 14 percent in the bloodstream of fire fighters after a fire. Carbon monoxide concentrations were not reported.

Indoor Carbon Monoxide Exposure

Indoor levels of CO have been studied by the General Electric Company[16] for two buildings in New York City. One was a high-rise apartment building straddling the Trans Manhattan Expressway; the other, a high-rise office building located adjacent to a midtown Manhattan street canyon. The study showed that indoor CO levels were directly related to nearby outdoor CO levels. While indoor concentrations "lagged behind" (in time) outdoor levels, there was "no significant difference in CO levels along the outside walls and inside the two structures." The G.E. study reported typical indoor and outdoor CO concentrations of from 4.6 to 11.5 mg/m^3 (4 to 10 ppm).

Shaplowsky et al.[54] have reported the results of CO levels inside 1820 houses throughout the United States. Their results showed that 16.8 percent had levels above 11.5 mg/m^3 (10 ppm). In a similar study conducted by Rench and Savage[52] in 80 households in Fort Collins, Colorado, concentrations in homes were recorded in the kitchen and family room around the dinner hour. Their measurements showed that over 6 percent of the households had CO concentrations greater than 11.5 mg/m^3 (10 ppm). The mean CO levels measured were 3.55 mg/m^3 (3.09 ppm) in kitchens and 2.01 mg/m^3 (1.75 ppm) in family rooms.

In a study conducted by Yocum et al.[90] CO measurements were made inside domestic buildings. They found that indoor CO levels increased more slowly than outdoor levels, but, once built up, indoor levels remained higher for a longer period of time. Thus, domestic premises have a tendency to entrap gaseous pollutants. Yocum et al. measured typical CO concentrations of 0.87 to 6.92 mg/m^3 (0.76 to 6.02 ppm).

The effect of smoking cigarettes on indoor CO levels has been investigated by Bridge and Corn[6] who measured CO during two experimental "parties." In one 145-m^3 (5120-ft^3) room containing 50 people, 25 people smoked 50 cigarettes and seven cigars in one and one-half hours. With a room air exchange rate of seven times per hour, CO averaged 8 mg/m^3 (7 ppm). During a second experiment in a 106-m^3 (3750-ft^3) room containing 73 people, 36 people smoked 63 cigarettes and 10 cigars in one and one-half hours, producing an average CO content of 10 mg/m^3 (9 ppm).

Hoegg[27] conducted experiments in a closed 25-m^3 chamber. He found that CO levels increased with the number of cigarettes smoked. Concentrations ranged from 11.5 mg/m^3 (10 ppm) for four cigarettes to 80 mg/m^3 (69.8 ppm) for 24 cigarettes.

Anderson and Dalhamn[3] measured CO concentrations due to smoking in a medium sized (80-m^3) meeting room. Fifty cigarettes were smoked in 2 hours. With six air changes per hour, initial levels were 2.3 mg/m^3 (2 ppm), and average peaks during smoking were 6.9 mg/m^3 (6 ppm).

In Harke's[21] experiments, 21 persons smoked two cigarettes each in enclosed office rooms, and within 16 to 18 minutes they produced 56.4 mg/m^3 (49 ppm) of CO in a 57-m^3 room. Ventilating the room decreased these concentrations by 80 percent. In the case of one person smoking 11 cigarettes in five hours in a 30-m^3 room, the CO concentration was less than 11.5 mg/m^3 (10 ppm).

Smoking in automobiles can produce significant CO concentrations. Harke et al.[22-26] conducted experiments in which cigarettes were smoked in a car within a wind tunnel. During the experiment, time spent smoking was varied, as was wind speed and ventilation. At 0 km/hr, with full ventilation, CO averaged 9.2 to 11.5 mg/m^3 (8 to 10 ppm); when six cigarettes were smoked intermittently, CO reached a maximum concentration of 34.5 mg/m^3 (30 ppm). When cigarettes were smoked continuously, one after the other, with no wind or ventilation factor, final CO levels were registered at 92 mg/m^3 (80 ppm). With wind and ventilation, however, CO remained at 5.8 to 6.9 mg/m^3 (5 to 6 ppm), with no increases observed. In all cases CO levels returned to base levels, even with no ventilation, within a few minutes after smoking stopped.

Srch[59] measured CO concentrations produced by cigarettes in a closed automobile with no ventilation. The test car was parked in an unventilated garage while two of four people smoked five cigarettes each in 1 hour. Carbon monoxide levels reached 104 mg/m^3 (90 ppm) in that time. Carboxyhemoglobin in the smokers rose from 5 to 10 percent; it rose from 2 to 5 percent in the two non-smokers present.

The U.S. Department of Transportation in 1973 conducted a study of cigarette-caused pollution on inter-city buses. Inside a stationary Greyhound bus with the engine off, vents open, and blower on, cigarettes were allowed to burn in the ashtrays. Tests conducted ranged from the "worst" case, where it was assumed that all 43 passengers smoked half the time, to the "realistic" case, where only the last 20 percent of the seats were allotted to smokers. After 30 minutes in the worst case, CO stabilized at 38.0 mg/m^3 (33 ppm). In the realistic case, CO stabilized at 20.7 mg/m^3 (18 ppm) after 43 minutes, with an outside level of 15.1 mg/m^3 (13 ppm).

Many other studies have been performed to determine indoor exposure levels of pollutants. A summary of the results of many experiments has been prepared by Sterling and Kobayashi[58] and by the EPA.[81]

EFFECTS OF METEOROLOGY AND TOPOGRAPHY

Meteorology governs the transport and dispersion of CO emissions in the atmosphere and thus has a strong influence on the ground-level CO concentrations detected at receptor points downwind of emission sources. Meteorological variables that determine CO transport and dispersion patterns include wind speed, wind direction, atmospheric stability, vertical mixing height, and ambient temperature.

Wind speed and direction influence the horizontal dispersion of CO emissions. Low wind speeds provide little dilution air, allowing CO emissions to build up, resulting in higher CO concentrations. Conversely, high wind speeds aid in the dispersion of CO emissions by increasing the amount of dilution that takes place, thus decreasing CO concentrations. Wind direction determines the direction of horizontal transport of CO emissions and consequently the impact that CO emissions from one area will have on air quality in another area. For wind directions crossing an urban area, an accumulation of CO emissions will occur in the downwind direction, such that mesoscale (1 to 10 km) CO concentrations will be highest at the downwind edge of the urban area. In the microscale regime (1 to 100 m), for a highway line source, wind directions nearly parallel to the highway will allow for an accumulation of CO emissions in the downwind direction, resulting in CO concentrations higher than would be expected for perpendicular winds under the same conditions.

In addition to transporting pollutants, winds produce turbulence in the atmosphere, which enhances the mixing and dispersion of pollutants in the air. Turbulence is the result of both mechanical forces and thermal forces in the atmosphere.

The effect of surface roughness (i.e., mountains, buildings, etc.) on the wind speed profile over several types of topographic features is illustrated in Figure 6-24.[2] With increased surface roughness, either natural or man-made, the wind speed profile is decreased and the depth of the affected layer is increased. The net effect of increased surface roughness over an urban area is to induce mechanical turbulence that aids in the dispersion of CO emissions.

Radiation and thermal properties of topographic features influence the heating and cooling of the atmosphere near the ground surface. The most notable of these effects is the urban "heat island" effect. Heat sources, including the asphalt and concrete associated with an urban area, tend to radiate heat, causing a "heat island" compared to the cooler surrounding terrain. The buoyant effect of warmer air over the city tends to induce thermal turbulence (i.e., more unstable atmospheric conditions), which tend to aid in the dispersion of CO emissions, thus lowering ambient CO concentrations.

Drainage winds, such as sea-land breezes, lake-land breezes, or mountain-valley winds, are caused by the differential heating of topographic forms. Drainage winds that affect net transport of CO emissions may deviate from the prevailing wind direction. These winds generally flow in one direction during the day, then in the opposite direction at night. As a result, an urban area can experience "blow-back" of CO emissions emitted during the day; these will be experienced as higher CO concentrations at night. Also, the boundary region of the drainage winds sometimes causes the air mass to remain nearly stationary, or to oscillate back and forth for periods up to several hours, and can be the site of nearly calm conditions or varying winds. These characteristics result in slow net transport of CO emissions which then accumulate and result in higher ambient CO concentrations.

Vertical mixing height affects the total ventilation capacity of the atmosphere. When the temperature-altitude relationship is reversed from normal, the resulting increase in temperature with increase in height produces an inversion or inversion lid that limits vertical mixing, and thereby limits the dilution capacity of the atmosphere.

An important form of inversion for CO dispersion is the surface or radiation inversion. This usually occurs at night with light winds and clear skies, when the loss of heat by long-wave radiation from the ground surface cools the surface and subsequently the air adjacent to it. The surface inversion usually persists for hours and, because it typifies stable atmospheric conditions, it tends to result in high microscale and mesoscale CO concentrations. With the proper relative humidity, these same conditions will lead to the formation of radiation fog. The presence of early morning fog is often associated with a surface-based temperature inversion.

Another type of inversion is the subsidence inversion. It is caused by a gradual descent of air aloft, accompanied by an increase in pressure that results in an adiabatic warming of the descending layer. The resulting subsidence inversion is illustrated in Figure 6-25, which shows the temperature decrease with height and the capping by a subsidence inversion layer,

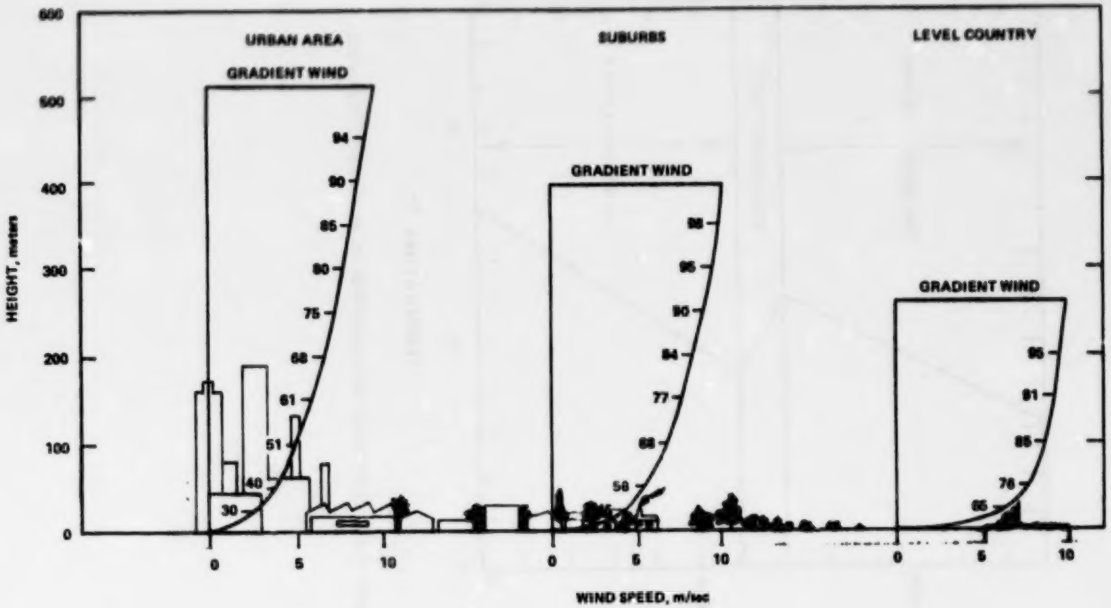

Figure 6-24. Effect of terrain roughness on the wind speed profile.

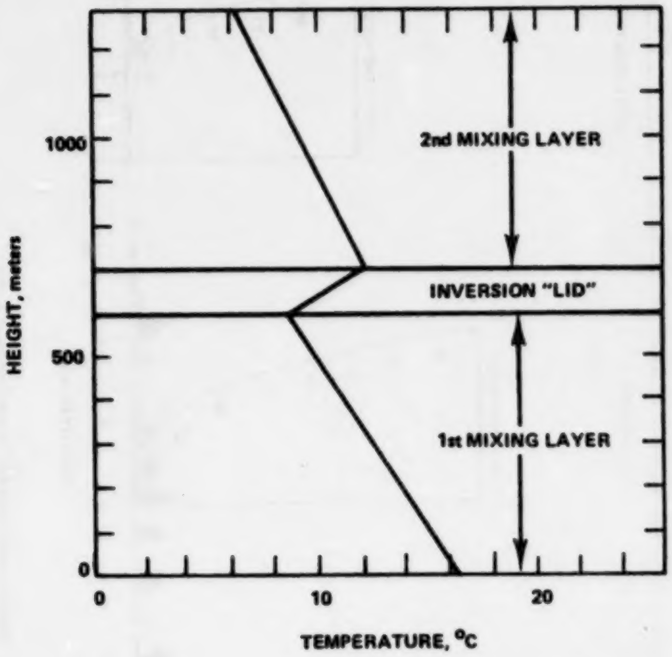

Figure 6-25. Schematic representation of an elevated inversion.

above which there is a normal decrease of temperature with height. The subsidence inversion usually persists for days and tends to contribute to high urban background CO concentrations. The subsidence inversion is usually more persistent during summer and fall than in winter or spring.

The shape of typical plots of hourly CO concentrations (see Figures 6-9, 6-10, and 6-11) can be attributed in large part to the effect of changing wind speeds, atmospheric stability, and inversion height during the course of a day. Figure 6-26 shows average hourly wind speeds and inversion heights occurring in Los Angeles during summer.[61] The higher wind speeds and inversion height during early afternoon are typical throughout the continental United States and play a significant role in lowering urban CO concentrations at midday. Figure 6-26 shows that traffic volumes, and subsequently CO emissions from cars, would still be expected to be high at this time of day. Around midnight, when traffic volumes are relatively low, the effects of low wind speeds and low inversion heights tend to cause increases in CO concentrations. Many monitoring stations in the United States observe these relatively high CO concentrations late at night.

In addition to transport and dispersion, ambient surface temperature also has a unique effect on the production rate of CO emissions from automobiles. Using a variety of automobiles tested at artificially controlled ambient temperatures of 20°, 50°, 75°, and 110°F, the EPA[13] found that lowest CO emissions were produced at 75°F. Colder temperatures seem to increase emission rates, resulting in higher ambient CO concentrations, while warmer temperatures minimize emission rates and result in lower concentrations.

CARBON MONOXIDE DISPERSION MODELS

A dispersion model relates pollutant emissions to ambient air quality by providing a mathematical description of the transport, dispersion, and chemical transformations that occur in the atmosphere. This ability to relate source emissions to receptor air quality is very important to air quality maintenance planning and environmental impact assessment.

Dispersion models vary in complexity from simple empirical or statistical relationships to sophisticated multi-source models that describe the transport and dispersion of CO throughout an urban area. For estimates of ambient CO concentrations, a line source model is needed to estimate the CO levels near a single source or group of sources, and an area source model is needed to estimate the background CO levels due to other sources. The types of models used, therefore, will depend mainly on the source configuration to be modeled (i.e., area, line, or point sources).

Model input data consist of parameters such as traffic volume, vehicle speed, truck mix, vehicle age (needed to estimate emissions); wind speed and direction, atmospheric stability class, receptor location; and source characteristics such as road location, road width, number of lanes, median width, etc. Typically, model output consists of tabulated results of input data and predicted CO concentrations. Some models can provide computer plots of results and isopleth maps showing the calculated spatial variation in CO levels.

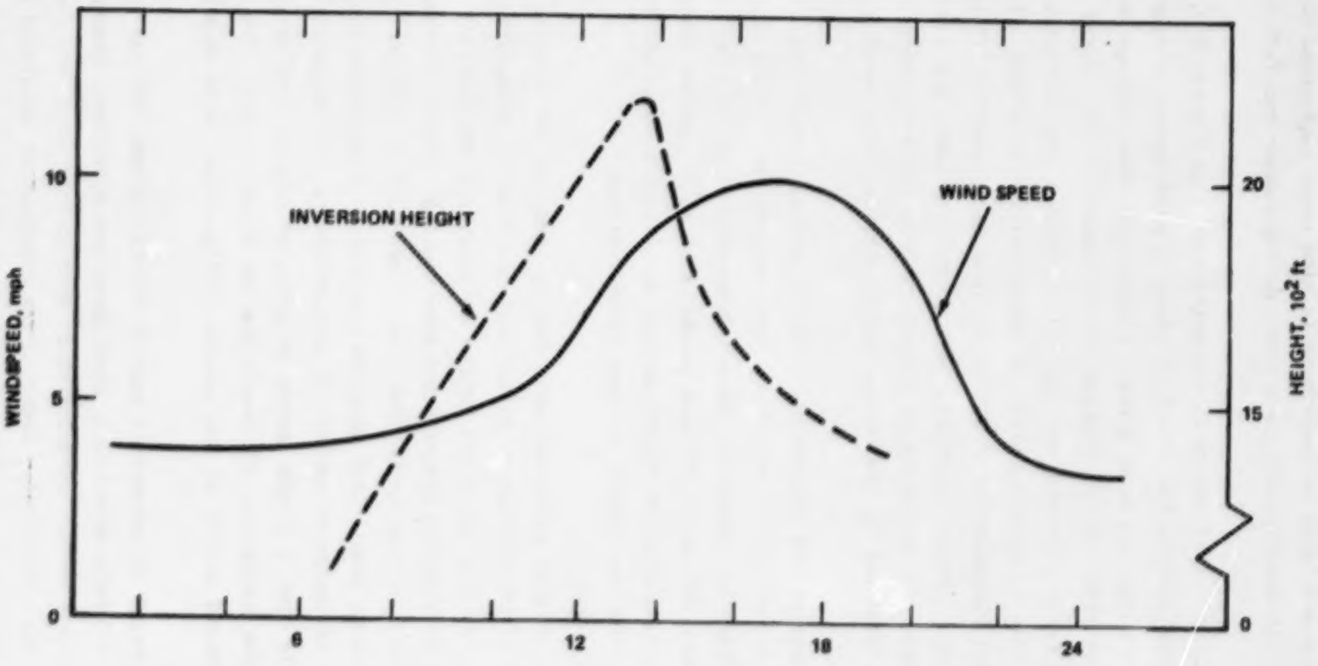

Figure 6-26. Hourly variations in inversions height and wind speed for Los Angeles in summer.

The rollback model[73] is a simple modeling technique that assumes a linear relationship between ambient air quality and area pollutant emissions. The use of rollback requires air monitoring data and emission inventories. Its main use has been to calculate the percent reduction of pollutant emissions needed to achieve an ambient air quality standard. It has also been used to predict future ambient pollutant concentrations by factoring air monitoring data by a ratio of projected future pollutant emissions to base year pollutant emissions. Rollback is widely used because it is simple and easily understood. In order to use the rollback method, ambient air monitoring is required to establish existing CO levels. For those areas without available monitoring data, an alternate modeling scheme would be necessary. Also, the rollback method incorporates the assumption that an overall proportional reduction of emissions in the area is required to meet the ambient air quality standard when, in some cases, a reduction in emissions at a few specific sources may be sufficient to meet the standards. Finally, the model provides little or no spatial resolution of ambient pollutant concentrations.

More sophisticated techniques for modeling background CO concentrations include the Hanna-Gifford model,[19,20] and APRAC-2.[36] In the Hanna-Gifford model, area source emissions are assigned to grid squares, and it is assumed that the area source strength is uniform across each square. Gifford's "reciprocal plume" concept is employed to estimate the surface concentrations due to area sources upwind of the receptor grid. The vertical distribution of the pollutant is assumed to be Gaussian. The spatial resolution of the model is on the order of kilometers. The authors of the model feel that it performs nearly as well as much more complex models that require the use of digital computers. Depending on the model application, correlations between predicted and measured pollutant concentrations ranging from 0.60 to 0.95[19] have been found.

The APRAC-2 dispersion model[36] uses a number of area segments spaced at logarithmic upwind intervals from a receptor point, as shown in Figure 6-27. This area segment scheme overlaps the coded traffic network from which traffic links and portions of links falling within each area segment are identified. The emissions from each individual link are then calculated and accumulated to determine the average emission rate for each of the nine area segments. Background CO concentrations are calculated from two basically different formulations. For sources near the receptor, a Gaussian model is used. A simple "box" model is used, under limited vertical mixing conditions, at the point of restricted vertical dispersion. The spatial resolution of the model is on the order of tenths of kilometers.

The APRAC-2 model also provides a choice of two special models for calculating CO concentrations from nearby highway sources: the street canyon model and the intersection model. The street canyon model is based on work by Georgii et al.[18] and the "San Jose experiment" by Ludwig and Dabberdt.[35] These studies showed that, because of lower wind speeds and a general helical circulation, higher CO concentrations on the leeward side of the street result because of the reverse flow component at ground level. The intersection model predicts

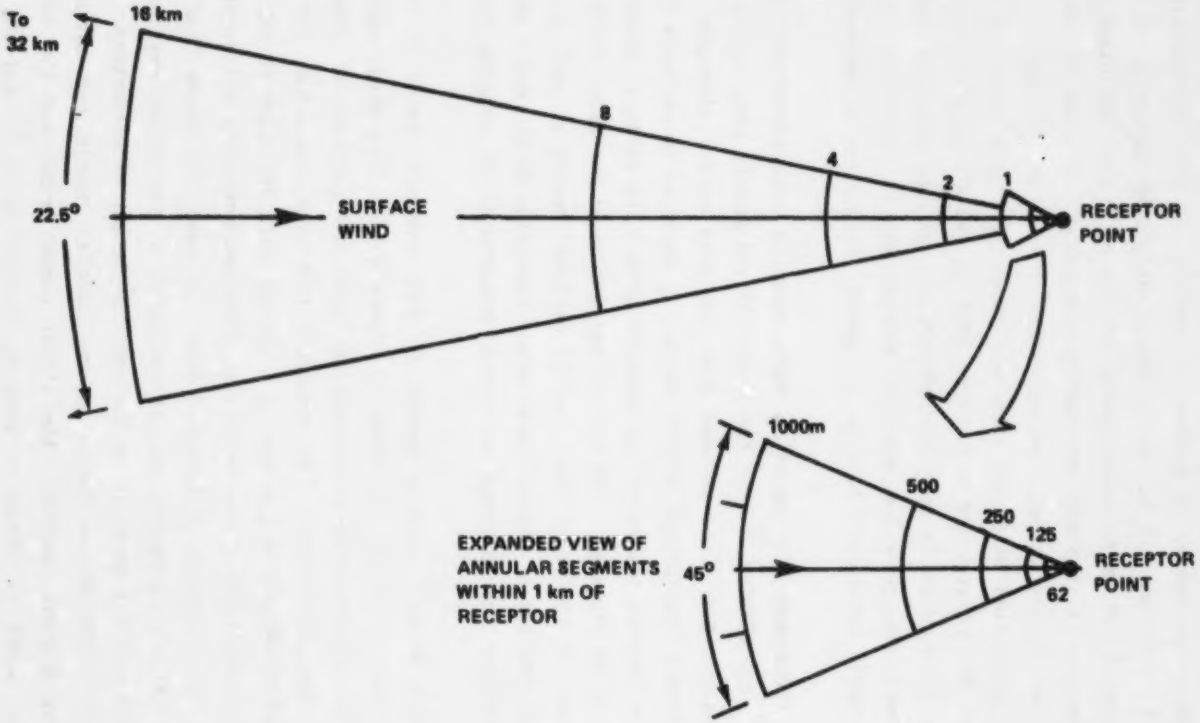
To
32 km
16 km
22.5°
SURFACE
WIND
8
4
2
1
RECEPTOR
POINT
1000m
500
250
125
62
45°
RECEPTOR
POINT
EXPANDED VIEW OF
ANNULAR SEGMENTS
WITHIN 1 km OF
RECEPTOR

Figure 6-27. Area segment scheme for spatial portioning of emissions.

CO concentrations in the vicinity of an intersection by combining a traffic model, a modal emissions model*, and a line source dispersion model. The line source model is based on an integrated point source technique.

Field experiments were performed in downtown St. Louis in 1971 to evaluate the performance of the APRAC-1A model.[38] Carbon monoxide concentrations were calculated at four locations within street canyons, and at two locations at roof level. These calculations were compared to about 600 1-hour average observations for each location. The observed concentrations of CO were simulated with root-mean-square errors of 3.5 to 4.6 mg/m^3 (3 to 4 ppm). Median and 90 percentile concentrations were specified within 2.3 to 3.5 mg/m^3 (2 to 3 ppm).[38]

The most widely used line source dispersion models are based on the Gaussian plume equations, namely HIWAY[76]--developed and distributed by the Environmental Protection Agency--and CALINE-2[28]--developed by the California Department of Transportation and distributed by the Federal Highway Administration. The HIWAY model uses an integrated Gaussian point source equation to calculate CO concentrations near a highway line source. The model approximates a line source by a finite number of point sources of emission strength equal to the total line source emission strength divided by the number of sources used to simulate the line. CALINE-2 uses an integrated Gaussian point source equation for the "pure" parallel wind case (i.e., 0° with respect to the highway) and a Gaussian line source equation for the "pure" crosswind case (i.e., 90° with respect to the highway). For wind directions that are neither 0° nor 90° to the highway, the model uses a trigonometric function to weight the parallel and crosswind terms. These line source models provide detailed spatial resolution between zero and 300 meters from the highway.

In addition to the mathematical differences between the two models, HIWAY uses a virtual source correction providing an initial dispersion height of 1.5 meters, while CALINE-2 assumes initial dispersion from a theoretical mechanical "mixing cell" at a height of 4 meters. The HIWAY model also uses dispersion coefficients that differ from the coefficients used by the CALINE-2 model.

A comparison of HIWAY and CALINE-2 model predictions is presented in Figures 6-28 and 6-29 for crosswind and parallel wind predictions, respectively.[46] These model predictions indicate that ambient concentrations near highways tend to be greatest at the roadside edge and to decrease with distance from the highway: typically, concentrations 300 meters from the highway may be only 20 percent as high as roadside edge concentrations. Noll et al.[46] found, from a comparison of predicted and measured concentrations, that HIWAY and CALINE-2 overestimate concentrations for parallel wind conditions and underestimate concentrations for oblique and crosswind conditions. Noll et al.[46] and Miller and Noll[43] report typical correlation coefficients for the models ranging from 0.5 to 0.85. Higher correlations have been reported, but for small sample sizes (i.e., less than 20).

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*-Kunselman et al.[30] have developed a model which can be used to describe air pollution emissions from automobiles as a function of operating mode (i.e., steady-state, acceleration, and deceleration).

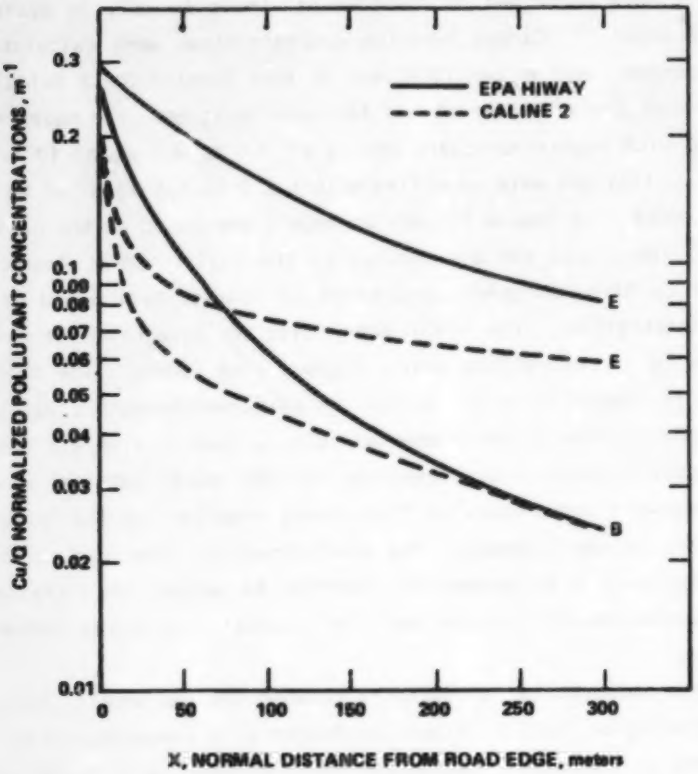

Figure 6-28. Normalized concentrations versus normal distance from the road edge for perpendicular wind conditions for B and E atmospheric stability category.

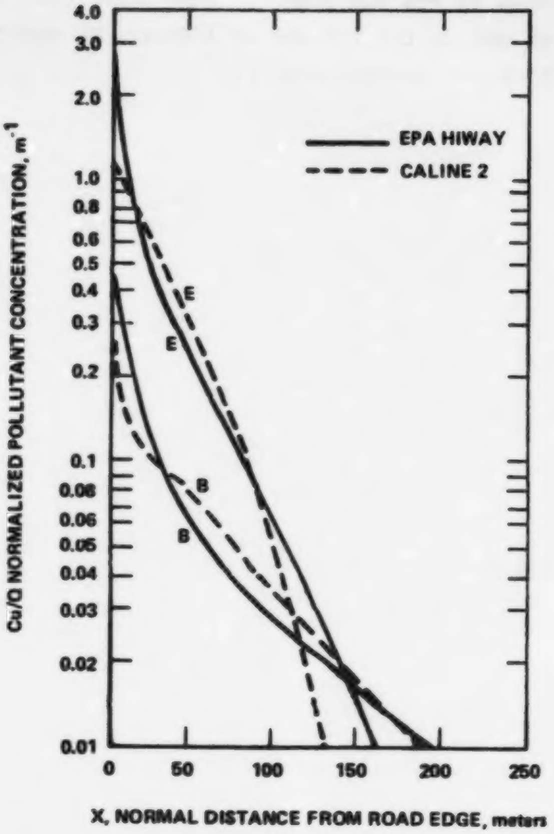

Figure 6-29. Normalized concentration versus normal distance to the road edge for parallel wind conditions for B and E atmospheric stability category.

Other line source modeling techniques include the numerical modeling approach and turbulent wake theory approach. Numerical models include those proposed by Ragland and Peirce,[51] Danard,[12] Sklarew et al.,[55] and Maldonado and Bullin.[39] Turbulent wake theory models include those proposed by Fay and King.[14] Some other Gaussian and pseudo-Gaussian models have been developed and tested for use on highways by General Motors[9] and by the Virginia Highway and Transportation Research Council.[7]

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7. THE GLOBAL CYCLE OF CARBON MONOXIDE

Although many studies in the last decade have been devoted to identifying and quantifying the various sources and sinks of carbon monoxide (CO) in the global atmospheric equation, there is still great uncertainty about the relative importance (of many) of the contributing sources to the global CO budget. The fundamental question is whether the origins of CO in the atmosphere are natural or anthropogenic. Research in the late 1970s suggests that human activities have significantly altered the background concentration of CO, especially in the Northern Hemisphere. The effects of such an alteration are complex, but most recent theories[6,12] speculate that the increase in background CO concentrations will have an important impact on tropospheric and stratospheric ozone distributions, as well as on the global budgets of several other trace gases.

INTRODUCTION

Prior to 1970, the sources of CO were thought to be well understood. For the most part, CO was thought to be produced by incomplete combustion of carbonaceous matter; any other source was thought to be small compared to production through combustion.[17] However, a new era of speculation evolved when Levy[23] proposed that the hydroxyl (OH) radical was present in the unpolluted troposphere in concentrations greater than 10^6 molecules/cm^3. With this OH number density, the observed clean air concentration of methane, and the measured rate constant governing the (CH_4 + OH) reaction,[14] it could be shown that a substantial quantity of CO is generated in the clean atmosphere if the methane oxidized by OH is converted to CO. According to this scheme, the methane oxidation source of CO was estimated as 10 to 25 times larger than the combustion source.[29,54] Thus, a new philosophy of atmospheric chemistry that included photochemical processes in the unpolluted troposphere (OH can be generated only through a photochemical sequence) developed in the 1970s.

More recent photochemistry calculations indicate that methane oxidation probably is not so large a source of CO as indicated by those first studies. Because of the uncertainties inherent in numerical models of photochemical processes and because relatively few measurements must be extrapolated to derive other global source terms for CO, no definitive conclusion can be drawn as to the dominant source of CO in the atmosphere. The more detailed discussion of CO sources in the following sections reviews many of the previous studies.

GLOBAL SOURCES

Technological Sources

Early inventories[17,32] of CO emissions focused on combustion sources because no significant natural source of any other type had been positively identified. Estimates of global CO emissions from fossil fuel combustion differ by more than a factor of two.[32,34] To derive the values, emissions from technological sources were computed by assessing the amount of coal and petroleum fuels produced in a given year and then multiplying that figure by previously determined conversion factors.[18] Emission rates calculated by this method were 2.6 x 10^{14} g/yr by Robinson and Robbins,[32] who used fossil fuel usage data from 1966, and 3.6 x 10^{14} g/yr by Jaffe,[18] who used 1970 data. In general, these investigators concluded that the automobile was the largest technological source of CO, and that emissions increased substantially during the years between the onset of widespread automobile use and 1970.[3] The Robinson and Robbins study showed that mobile sources were responsible for 68 percent of CO emissions; Jaffe's estimate was 70 percent.

Seiler[34] has presented the most detailed analysis to date on the global cycle of atmospheric CO. He contends that the previously estimated CO emission rates are lower limits. He cites the fact that the home heating source of CO in West Germany was shown to be as much as 30 percent of the automobile source, whereas Jaffe's calculations had used a relative home heating contribution of less than 1 percent. Furthermore, Seiler contends that several industrial sources, such as ammonia and methanol reforming facilities, synthetic gas and organic chemical manufacturing plants, and other possible emitters of CO, were not considered in previous inventories. Thus, Seiler's[34] calculation of technological CO emissions is 6.4 x 10^{14} g/yr, about two times greater than Jaffe's estimate. Aircraft data subsequently obtained over Munich and extrapolated for the globe suggest a total technological source ranging from 6 x 10^{14} to 10 x 10^{14} g/yr.[44]

In addition to direct emission of CO, the oxidation of nonmethane hydrocarbons given off by automobiles may be considered an indirect technological source of CO. Although no quantitative estimates of this potential source have been published, it is possible that if most of the carbon contained within the hydrocarbons emitted in an urban area[52,53] were converted to CO, a source strength equal to nearly half of the direct CO emissions would be accounted for. The mole-to-mole conversion rate to CO of certain hydrocarbons found in automobile exhaust has been observed to exceed 0.4[1] in smog chamber studies. Although the magnitude of this source has never been computed in detail, it may be equivalent to a sizable fraction of the amount of CO released directly to the atmosphere in automobile exhaust.

Natural Sources

Forest Fires and Agricultural Burning--Because combustion processes then appeared to be the only mechanism by which CO was produced, the early emission inventory studies of Robinson and Robbins[32] and Jaffe[18] assumed that natural releases of CO, if they occurred, likewise originated from combustion of carbonaceous matter. To date, however, forest fires and agricultural burning have not been shown to be significant sources of atmospheric CO. The estimated CO emissions from these natural sources range from 0.1 x 10^{14} g/yr[32] to 1.5 x 10^{14} g/yr.[36]

Carbon Monoxide Production from Oceans--Analyses of ocean water[20,41,42,48,49,50] often indicate supersaturated quantities of CO. The highest supersaturation factors have been found in nutrient-rich waters and are believed to be a result of microbiological activity. Thus, the ocean acts as a source of atmospheric CO; its strength has been estimated to lie between 0.2 x 10^{14} g/yr and 2.0 x 10^{14} g/yr.[27,42,50]

Oxidation of Natural Hydrocarbons--Carbon monoxide is produced by photochemical oxidation of naturally occurring hydrocarbons and chlorophyll. Went[56] pointed out that the apparent lifetime of terpene-like hydrocarbons in the atmosphere does not appear to be very long. Concentrations of these compounds range between 2 and 20 ppb (parts per billion),[31] from which Went[57] estimated a global emission rate of 10×10^{14} g/yr for such volatile organic compounds. Robinson and Robbins[32] estimated from these data that 0.6×10^{14} g/yr of CO could be produced. Their calculation is based on the assumptions that one molecule of CO is produced from three molecules of organic matter[21] and that the average organic molecular weight is 150.

More recent studies, however, suggest that oxidation of naturally emitted hydrocarbons from vegetation results in a global CO source ranging from 4×10^{14} to 13×10^{14} g/yr.[36,62] Derivation of the CO source strength from this process requires the inclusion of many assumptions, and, therefore, it is fair to say that the amount of CO produced from naturally emitted hydrocarbons is not definitely known. Many more laboratory and field studies will be required to reduce uncertainty about the strength of this source.

Emission by Plants--Wilks[59] reported that green plants grown in a clean illuminated environment liberate small quantities of CO as well as certain aldehydes. Although Siegel et al.[45] showed that CO was given off by plant material in the dark, it could not be ascertained whether the CO was emitted directly or was formed as a result of photolysis of the aldehydes. Further investigation of these phenomena by Seiler et al.[38] showed that plants contribute 0.7×10^{14} g/yr to global CO concentrations. This estimate was obtained from in situ measurements observed from four different C_3-type plants and was found to increase as the radiation intensity increased.

Methane Oxidation--When Levy[23] proposed that sufficient concentration of the OH radical could exist in the troposphere to produce quantities of formaldehyde (CH_2O) on the order of 2 ppb from methane oxidation, it was easy to show that significant quantities of CO could be formed through CH_2O degradation. Every known important homogeneous process that removed CH_2O from the troposphere results in direct formation of CO:

$$CH_2O + h\nu \rightarrow CO + H_2,$$

or

$$CH_2O + h\nu \rightarrow H + HCO,$$

and

$$CH_2O + OH \rightarrow H_2O + HCO,$$

rapidly followed by $HCO + O_2 \rightarrow CO + HO_2$.

The oxidation of methane (CH_4) in the troposphere may proceed as follows:[5,61]

$$\begin{aligned} CH_4 + OH &\rightarrow CH_3 + H_2O, \\ CH_3 + O_2 + M &\rightarrow CH_3O_2 + M, \\ CH_3O_2 + NO &\rightarrow CH_3O + NO_2, \\ \text{and}\quad CH_3O + O_2 &\rightarrow CH_2O + HO_2. \end{aligned}$$

Once OH attacks a methane molecule, the subsequent reactions proceed very rapidly, and thus the limiting factor in the production of CO is the initial rate of the (CH_4 + OH) reaction.

The net result of the above demands that the amount of methane oxidized in the troposphere is the same molar quantity as the CO produced from this process.

Table 7-1 summarizes many of the studies that have been conducted to determine the various source strengths of atmospheric CO. Of primary importance is the fact that the first estimates of CO production from methane oxidation[24,29,54,61] showed that this source was five to 20 times larger than the anthropogenic sources estimated by Robinson and Robbins,[32] whose study was the only comprehensive CO source inventory available at the time of the initial methane oxidation calculations. In all the photochemical studies cited above, globally and diurnally averaged OH radical number densities ranged between $1 \times 10^6/cm^3$ and $3 \times 10^6/cm^3$. Similar calculations were made later by Weinstock and Chang[55] and Wofsy.[60] However, those studies employed several key reaction rate constants that were subsequently shown to be inaccurate. In particular, the reaction rate governing the OH radical's attack on CO (discussed in detail in Section 3.3) was reported in later studies[4] to be pressure-dependent and to be more than twice as fast at tropospheric pressures as the rates measured prior to 1976. Since this reaction dominates all others in determining the destruction frequency of OH in the troposphere, a factor-of-two increase in its rate results (to a first approximation) in a factor-of-two decrease in the average amount of OH calculated by earlier numerical models.

Crutzen and Fishman[6] and Fishman and Crutzen[11] have presented numerical analyses that incorporate the more recent chemical kinetic data. In their reports, they address some of the uncertainties inherent in the determination of rates of photochemical production and destruction of CO and other trace gases. In the 1977 paper, Crutzen and Fishman point out that the methane oxidation reaction sequence may be broken and no CO produced from it if peroxides are formed and then removed from the atmosphere by a rapid heterogeneous process. Under such an assumption, as little as 0.6×10^{14} to 4.0×10^{14} g/yr of CO would be produced as a result of methane oxidation. Similarly, Seiler[35] calculated a value of 4×10^{14} g/yr for methane oxidation. Anthropogenic CO source strengths calculated by Seiler[34,35,36] are two to five times higher than previous calculations by Jaffe[18] and Robinson and Robbins.[32] Thus it now appears that methane oxidation is no longer believed to be the dominant source of atmospheric CO as it was in the early 1970s.

Other Natural Sources--Swinnerton et al.[47] have reported very high supersaturation values of CO in both rainwater and cloud droplets. Furthermore, rainwater samples in both unpolluted regions (Hawaii) and polluted regions (Washington, D.C.) showed excessive amounts of CO. The mechanism for this phenomenon is not well understood, but two possible explanations are the dissociation of carbon dioxide by electrical discharges and the photolysis of aldehydes dissolved in the droplets. Quantification of this source on a global scale has been attempted by Seiler,[34] but there are too many uncertainties to produce a number accurate to more than several orders of magnitude. Thus, production of CO in cloud droplets or rainwater is probably not a significant source of CO in the atmosphere.

TABLE 7-1. GLOBAL CARBON MONOXIDE SOURCE STRENGTH ESTIMATES
(10^{14} g/gr)

Reference	Fossil fuel	Forest fires	Methane oxidation	Oxidation of hydrocarbons	Oceans	Plants
Seiler, 1974[34]	6.4	0.6[a]		0.6	1.0	
Robinson & Robbins, 1969[32]	2.5	0.1		0.6		
Jaffe, 1973[18]	3.2	0.4				
Seiler, 1976[35]			4		0.4	0.2-2.0
Seiler & Zankl, 1976[44]	6-10					
McConnell et al., 1971[29]			27			
Weinstock & Niki, 1972[54]			50			
Wofsy et al., 1972[61]			15			
Levy, 1973[24]			33			
Weinstock & Chang, 1976[55]			38[b]			
Wofsy, 1976[60]			14			
Crutzen & Fishman, 1977[6]			0.6-4.0[b]			
Fishman & Crutzen, 1978a[11]			2.9-7.4[b]			
Zimmerman et al., 1978[62]				4-13		
Stevens et al., 1972[46]				2.0-5.0[c]		
NAS, 1977[30]				0.5		
Swinnerton et al., 1970[50]					0.2	
Linnenbom et al., 1973[27]					2.0	
Liss & Slater, 1974[28]					0.4	
Seiler & Schmidt, 1974[42]					0.7	
Seiler & Giehl, 1977[37]						0.5
Seiler et al., 1978[38]						0.5-1.0
Range of estimates	2.5-10	0.1-0.6	0.6-50	0.5-13	0.2-2.0	0.2-2.0

[a] Includes agricultural burning

[b] Global values derived by doubling Northern Hemisphere values reported in these studies.

[c] Northern Hemisphere estimate.

Other natural CO sources have been found, but to date, none of them is believed to contribute significantly to the global budget. Green et al.[13] showed that CO could be produced by charged-particle deposition mechanisms and atmospheric discharge phenomena, including cloud corona discharges, background radioactivity, natural electrostatic discharges, photoelectrons in the ionosphere, auroral electrons and protons, cosmic rays, and solar wind. The decomposition of hemoglobin in animals also results in CO production,[34] as does volcanic activity. Above 70 km, photodissociation of carbon dioxide (CO_2) is a source of CO.

BACKGROUND LEVELS AND FATE OF CARBON MONOXIDE

Measured Background Levels of Carbon Monoxide

Geographic Distribution--A distinct latitudinal variation in background concentrations has been observed by both Wilkness et al.,[58] in measurements over the Pacific Ocean, and Seiler,[34] in measurements over the Atlantic Ocean. Seiler's values, shown in Figure 7-1, are averages based on the integrated concentrations during 1969 sampled between the surface and the tropopause. Integration of these data for each hemisphere shows that more than twice as much CO is present in the Northern Hemisphere than in the Southern Hemisphere. Robinson and Robbins[33] report average mixing ratios of 140 ppb for the Northern Hemisphere and 60 ppb for the Southern Hemisphere. These concentrations have been reconfirmed by Seiler's later and more extensive work.

Seiler[34] points out that the background mixing ratios in the Southern Hemisphere remain very constant. The standard deviation of CO concentrations in a region between 50 and 65° S and 30 and 80° W over a three-month period was less than 3 percent. Carbon monoxide variations are largest in the North Atlantic and are attributed to the passage of continental plumes from North America. A relatively sharp difference in mixing ratios was quite often observed within the Trade Wind inversion layers on either side of the intertropical convergence zone in both the Atlantic and the Pacific.[34,58]

The considerably higher average CO concentration in the Northern Hemisphere, where 90 percent of the anthropogenic emission sources are located, does not support the hypothesis that CH_4 oxidation is the dominant source of CO, as was proposed by the National Academy of Sciences.[30] Since CH_4 is evenly distributed throughout the world,[18] the magnitude of the CH_4 oxidation source of CO should be nearly equal in both hemispheres. Furthermore, if the anthropogenic CO source is only 10 percent of the natural source,[30] such a small difference in the overall source strengths in the two hemispheres should result in a much smaller interhemispheric gradient. Although the inclusion of CH_4 oxidation as a source of CO is necessary to develop a clear picture of the global CO budget, its magnitude relative to other sources, on the basis of the current distribution of CO, remains to be assessed.

Variation with Height--Seiler and Junge[40] and Seiler and Warneck[43] showed that CO mixing ratios decreased sharply above the tropopause. They measured mixing ratios of less than 40 ppb at an altitude less than one km above the tropopause, in contrast to values between 130 and 160 ppb measured just below the stratospheric boundary in the northern mid-latitudes.

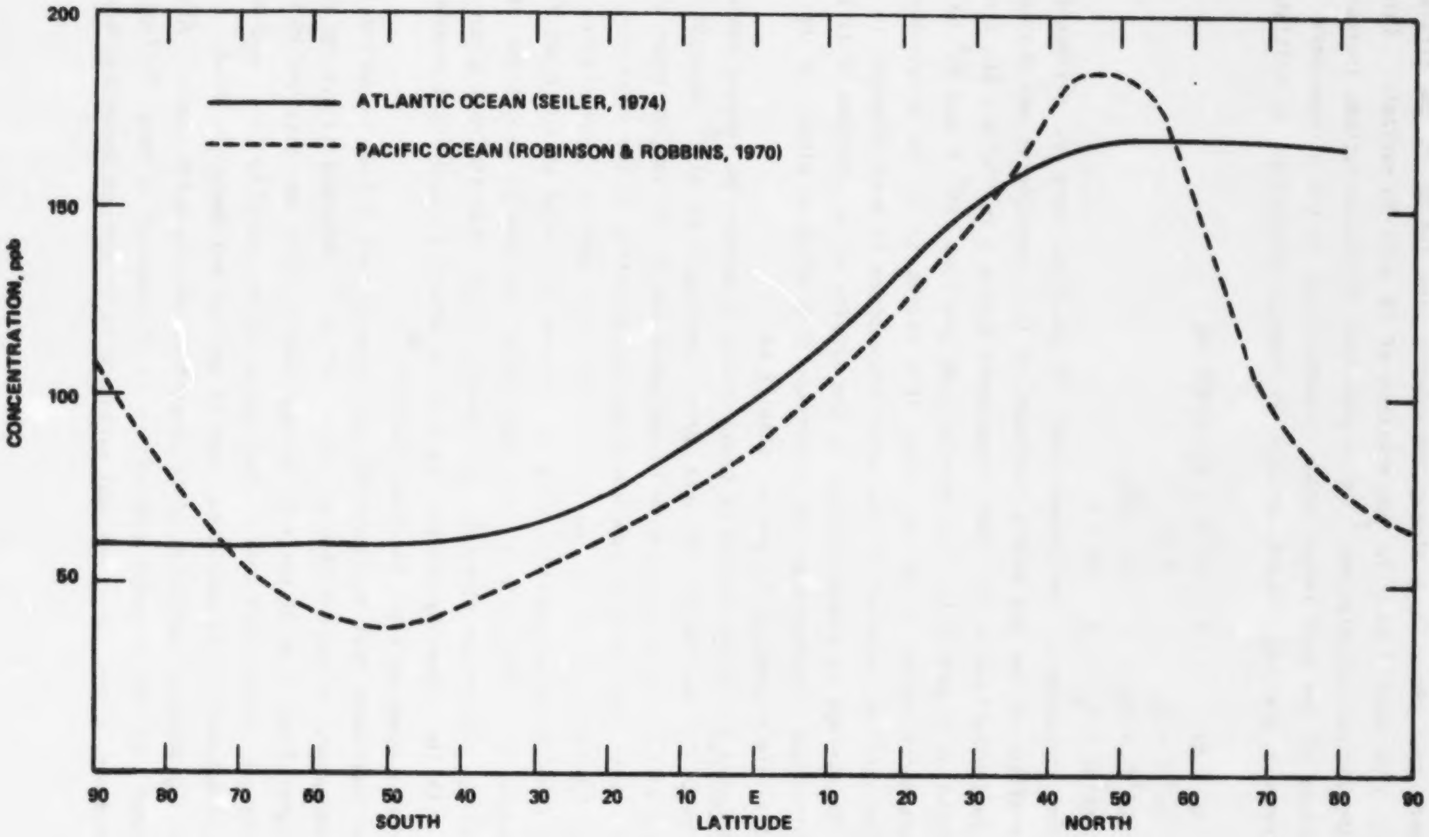

Figure 7-1. Latitude distribution of carbon monoxide. (Used with permission of Tellus 26:116-135.)

Thus, it appears that there is a strong atmospheric sink for CO in the stratosphere; the nature of this sink most likely is the reaction of CO with OH radicals. This belief is supported by theoretical calculations,[7] which show that OH concentrations increase above the tropopause because of the much larger ozone concentrations in the stratosphere. The larger ozone concentrations are significant because OH radical production is initiated by ozone photolysis:

$$O_3 + h\nu \rightarrow O(^1D) + O_2,\ \lambda<320\ \text{nm},$$

followed by $O(^1D) + H_2O \rightarrow 2\ OH,$

$$O(^1D) + CH_4 \rightarrow OH + CH_3,$$

or $O(^1D) + H_2 \rightarrow OH + H.$

Within the troposphere, background-level CO profiles vary at different latitudes. Tropospheric profiles at low and middle latitudes of both hemispheres are depicted in Figure 7-2. The CO concentrations in the lower troposphere (below 3 km) reflect the strong latitude gradient depicted in Figure 7-1. The mid-latitude profiles (45° N and 45° S) fall off to typical stratospheric values at 12 km, since this height is in the stratosphere at these latitudes. The vertical gradient in the upper troposphere is much stronger in the Northern Hemisphere. The average CO concentrations in the tropics at an altitude of 12 km are higher than the mid-latitude concentrations at a corresponding altitude since, in the tropics, the average height of the tropopause is greater than 12 km.

Diurnal and Seasonal Variation--During an ocean cruise to measure background concentrations of trace constituents in the Pacific in June 1970, Lamontagne et al.[20] reported a consistent diurnal pattern of CO concentrations both in sea water and in air samples taken just above the ocean surface. Both sets of data show a maximum concentration in the afternoon, when concentrations were typically 20 to 40 ppb higher than the average concentration of 130 ppb. However, this finding is inconsistent with our present knowledge of CO fluxes from the ocean into the atmosphere. Thus, the diurnal amplitudes reported by Lamontagne et al.[20] would imply a global oceanic source strength considerably larger than the ones given in Table 7-1. In agreement with the latter hypothesis, failure to detect a significant diurnal cycle of CO concentration over ocean surfaces has been reported.[34,50]

Using an instrument that monitored CO continuously over a 9-month period in Hawaii (at Mauna Loa Observatory, elevation 3400 m), Seiler et al.[39] detected an average diurnal cycle. A slightly higher (less than 10 percent) average concentration was observed in the afternoon. From these data, it appears that this diurnal cycle may be caused by local sources in combination with local meteorological phenomena, such as upslope and downslope winds.

Data showing seasonal variation of CO concentrations are quite scarce. Although Stevens et al.[46] showed that the isotopic composition of CO measured in rural Illinois exhibited a seasonal dependence, a conclusive seasonal variation in background concentrations could not be established.

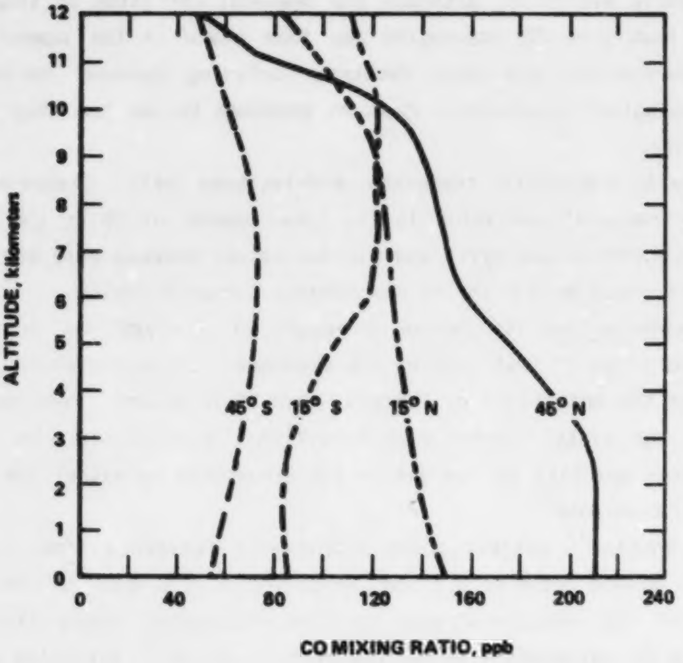

Figure 7-2. Latitudinal profiles of carbon monoxide.

Analysis of data collected by continuous monitoring during 1975 and 1976[39] at Mauna Loa Observatory in Hawaii (19.5° N) indicates that background CO concentrations are highest in the spring (March and April). The highest average values (120 to 130 ppb) are considerably greater than those measured in late summer (70 to 80 ppb). A good explanation of these observations is not readily available, although the seasonal variation of tropospheric OH concentrations suggests that more CO scavenging may take place in the summer. However, such an explanation is speculative, and other factors, including seasonal variation of large- and small-scale meteorological parameters, must be examined to see how they could influence the Hawaiian measurements.

In the Northern Hemisphere temperate mid-latitude belt, Dianov-Klokov et al.[8] have reported a similar seasonal variation in the total amount of CO in the U.S.S.R. They also find maximum values in March and April and minimum values between July and September.

Residence Time and Removal Mechanisms of Atmospheric Carbon Monoxide

Carbon Monoxide Residence Time--To derive a budget of a trace gas in the atmosphere, all possible sources and sinks of that species are examined. If no increasing or decreasing trend is detected for the concentrations of the gas, then it is assumed that the sum of the sources equals the sum of the sinks. Under such conditions, a residence time can be computed by dividing the measured quantity of the gas in the atmosphere by either the total emission rate or the total destruction rate.

Robinson and Robbins[32] estimated the atmospheric residence time of CO by assuming an average atmospheric mixing ratio of 0.1 ppm, which yields a CO mass in the atmosphere of 5.6×10^{14} g. Division of the calculated mass by their estimated source strength at 3.2×10^{14} g/year results in a CO residence time of 1.8 years. Seiler[35] estimated a residence time of 0.3 year. From the wide range of published source strengths summarized in Table 7-1, a CO residence time ranging from 0.07 to 1.38 years can be computed.

Removal Processes for Carbon Monoxide--The mechanisms by which CO is removed from the atmosphere are summarized by Seiler[34] and the National Academy of Sciences;[30] these studies concluded, after considering the possible CO sinks, that the major destruction term in the CO budget is oxidation by the OH radical. More recent reaction rates measured for the (CO + OH) reaction discussed in Chapter 3 indicate that the magnitude of this sink is probably twice as large as the values indicated in these two previous reviews if the globally averaged concentration of OH is the same as in these previous studies.

The Stratosphere as a Sink for Tropospheric Carbon Monoxide. As previously mentioned, CO mixing ratios decrease sharply above the tropopause.[41,43] From the average concentrations measured on either side of the tropopause, a theoretical calculation of the CO flux into the stratosphere can be made if the atmospheric diffusion coefficients in the region are known. Using this methodology, Seiler[34] derived a tropospheric CO loss rate of 1.1×10^{14} g/year by migration into the stratosphere. Because of the large difference in the average CO concentrations above and below the tropopause in the Northern Hemisphere (see Figure 7-2), 0.9 x 10^{14} g/year enter the stratosphere north of the equator, while only 0.2 x 10^{14} g/year migrate to the upper atmosphere in the Southern Hemisphere.

Soil as a Sink. Levy[22] showed that non-sterile soil rapidly depleted CO from test atmospheres containing initial concentrations of 100 ppm. The effect of this removal process was enhanced by increasing the soil temperature, but was eliminated by sterilizing the soil. The latter finding suggests that the biological activity of microorganisms in the soil is responsible for CO removal.

Ingersoll et al.[15] likewise found that soil was potentially a major sink of CO, but their studies showed that the soil uptake rate reached a maximum at 30°C and decreased at higher and lower temperatures. At 0°C the uptake rate was negligible, whereas at 50°C the uptake rate was less than 10 percent of that at 30°C. Seiler[34] indicated that at 50°C, CO was given off from the soil rather than taken up by it.

The studies of Levy[22] and Ingersoll et al.[15] concluded that the magnitude of the soil sink was considerably larger than the anthropogenic source of CO. However, Seiler[34] points out that the soil uptake rate is linearly dependent on the concentrations of CO in the atmosphere directly above the surface, and thus both estimates are too high because unrealistically high initial CO concentrations were used in the experiments. Using an initial atmospheric concentration of 0.2 ppm over the continent, Seiler estimated a global CO sink of 4.5 x 10^{14} g/yr due to soil uptake. Later studies[26,37] with different types of soil supported the sink strength estimated by Seiler.[34]

Such an estimate, however, is extremely crude[34] because of variations observed in the CO equilibrium concentrations above the soil, in the different types of soil, and in soil temperatures. For example, Inman et al.[16] point out that soils from different locations exhibit an eightfold variability in their ability to remove CO under the same laboratory conditions. Seiler[34] even speculates that some soils may act as sources rather than sinks of CO. It is clear that more research is needed before the role of soil on the global CO cycle can better be quantified.

Vegetation. The role of vegetation in the global CO cycle is currently not well understood. Some researchers have suggested that plants are a source of atmospheric CO;[37,45,59] but others have indicated that CO is absorbed by vegetation. For example, Krall and Tolbert[19] exposed barley leaves to an artificial atmosphere containing CO and determined that some of it was converted to serine and other compounds. Similarly, Bidwell and Fraser[2] investigated the incorporation of carbon-14 from an artificial CO atmosphere into plant carbon compounds. Seven of nine plant species were observed to take up CO. Extrapolation of these data indicates that plants are a significant sink for atmospheric CO, absorbing as much as 7 x 10^{14} to 70 x 10^{14} g/yr.

More recently, Seiler and Giehl[37] and Seiler et al.[38] concluded that the study of Bidwell and Fraser[2] is not a true measure of the net CO exchange rate between plants and the atmosphere. They point to the fact that the Bidwell and Fraser experiment is useful only to detect the amount of CO going into the plant and note that the large artificial CO concentrations used in the laboratory environment precluded accurate measurement of any CO coming back into the atmosphere. On the other hand, the method of Seiler and Giehl enables them to detect only the net influence of plants on atmospheric CO; they cannot distinguish the production from the uptake rates of the plants. Their findings indicate that vegetation is a net source of about 0.5×10^{14} g CO/yr when both production and uptake processes are taken into account.

Reaction with Hydroxyl. Estimates of the amount of CO removed from the atmosphere by reaction with OH indicate that this mechanism is the primary removal process for atmospheric CO.[6,34,35,60] If the amount of CO in the atmosphere is known, the global destruction rate as a function of the OH distribution can easily be computed. Similarly, if the distribution of CH_4 in the atmosphere is known, the amount of CO produced by methane oxidation can be calculated as a dependent variable of the average amount of OH present in the atmosphere.

Figure 7-3 shows graphically the results of such a simple calculation, in which the following parameters are assumed: CH_4 and CO mixing ratios of 1.4 ppm[9] and 0.1 ppm, respectively;

$$k_{CO+OH} = 2.5 \times 10^{-13} cm^3/(molecule \cdot sec); \text{ and}$$

$$k_{CH_4+OH} = 4.8 \times 10^{-15} cm^3/(molecule \cdot sec).$$

When the above values are used, the ratio of the rate of photochemical destruction of CO, D(CO), to the rate of photochemical production of CO, P(CO), is 3.7. This ratio is a lower limit, since it depends on the assumption that every CH_4 molecule oxidized results in the production of a CO molecule. Such a ratio demands that no more than 27 percent of the CO produced in the atmosphere comes from CH_4 oxidation. Furthermore, such a ratio is totally independent of the amount of OH in the atmosphere.

Although the D(CO)/P(CO) ratio is not affected by the average OH concentration, the magnitude of each of these terms clearly is affected (see Figure 7-3). Since about 90 percent of these terms is derived from tropospheric photochemical activity,[60] the average OH number density on the abscissa refers to a tropospheric value. Although previous studies derived information about the CO budget from calculated OH distributions,[6,60] the simple analysis depicted by Figure 7-3 can provide some useful insights into the global distribution of OH. For example, Seiler's[35] inventory of CO sources shows that 13.2×10^{14} g/yr of CO are emitted to the atmosphere. If it is assumed that the only CO sink is reaction with OH, then an average OH concentration of 3.6×10^5/cm will destroy CO at a rate of 13.2×10^{14} g/yr more than it can produce from methane oxidation.

Other Removal Processes. Carbon monoxide adsorption onto atmospheric particulate matter has been reported by Liberti.[25] His analyses indicate that adsorption by dust that is subsequently deposited on the earth's surface could be an important removal mechanism for ambient CO. The potential of this possible sink is not known. Further studies are necessary to

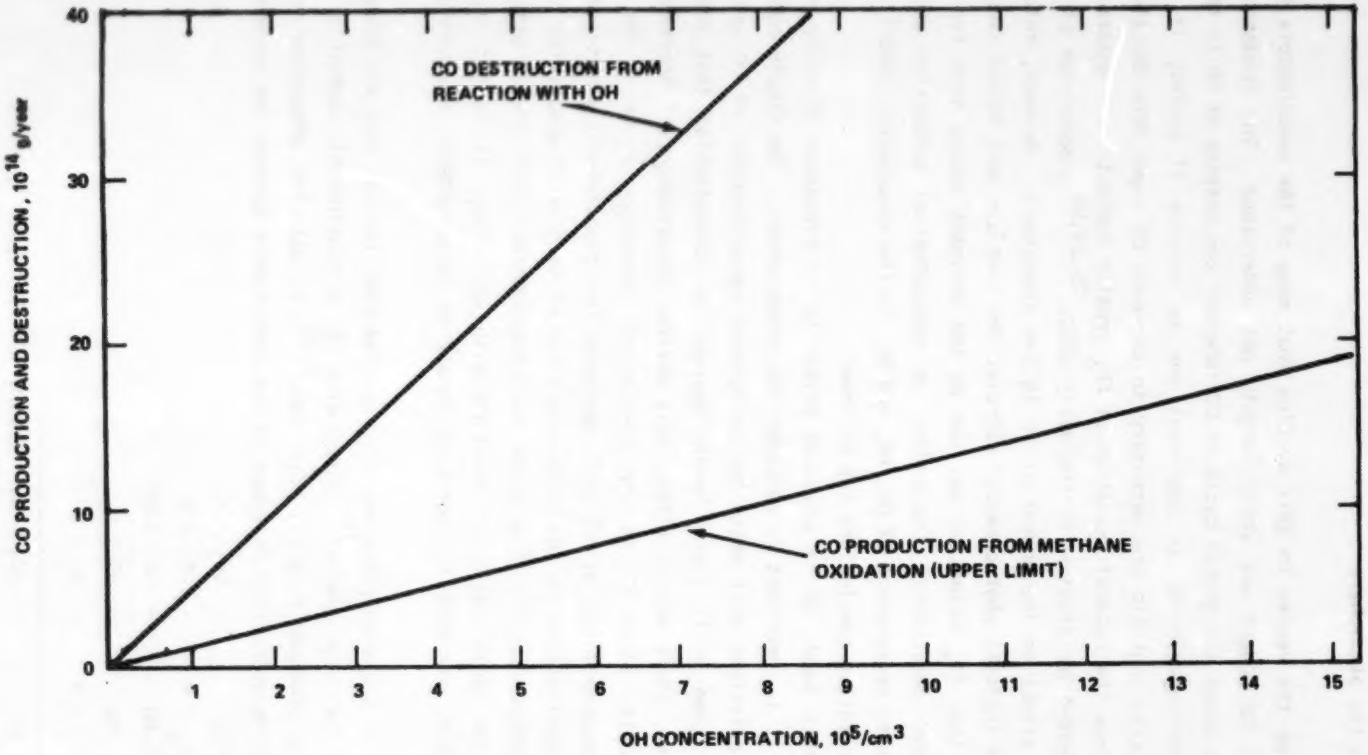

Figure 7-3. Carbon monoxide photochemical production and destruction rates as a function of average OH concentration.

determine the adsorption efficiency of different aerosol materials for the varying concentrations of CO found in the atmosphere.

SUMMARY

It is clear from the review in this section that many of the contributors to and components of the global CO budget are still largely not understood. The fundamental question raised in the 1970s about the global cycle of CO--whether the origins of CO in the atmosphere are natural or anthropogenic--is an important one to resolve if society is to determine whether or not emission controls are necessary to decrease CO input into the atmosphere. If the CO production from the natural oxidation of CH_4 greatly dominates all anthropogenic input terms, as was suggested by studies in the early 1970s,[24,29,54] suppression of CO emissions should have little effect on the amount of CO in the atmosphere. However, reformulation of the CO budget, which includes photochemical calculations that use more recent chemical kinetic information, shows that CH_4 oxidation may not be the dominant source term for CO.[6,35] The verification of these theoretical discussions on photochemical production and destruction rates of CO awaits more measurement of OH, NO, and NO_2 in the atmosphere. Until such data are available, no authoritative conclusions can be drawn.

If, on the other hand, CO is produced primarily by processes directly or indirectly controlled by man, it is important to consider the consequences. The simple answer is to say that anthropogenic emissions will raise the background concentrations of CO and that no substantial harm will come until these levels approach a concentration that endangers man's environment. However, there may be other, less obvious consequences of increased CO concentrations. For example, since CO is the predominant scavenger of OH in the troposphere, increased global concentrations of CO will decrease the tropospheric quantities of OH. In turn, lesser OH concentrations in the troposphere may allow greater quantities of trace gases such as CH_4[51] and methyl chloroform[6] to enter the stratosphere, since the primary tropospheric removal mechanism for these gases is reaction with OH. Thus, it is not impossible that increased CO emissions may have an important impact on stratospheric photochemistry and the ozone layer.

The fate of CO in the atmosphere may also provide some insight into the budget and distribution of ozone in the troposphere.[12] Along with CO, a considerable amount of tropospheric ozone may likewise be produced from CH_4 oxidation.[5,10] In addition, photochemical degradation of CO may produce large quantities of ozone in the troposphere through the sequence:

$$\begin{array}{lcl}
CO + OH & \rightarrow & CO_2 + H, \\
H + O_2 + M & \rightarrow & HO_2 + M \\
HO_2 + NO & \rightarrow & NO_2 + OH \\
NO_2 + h\nu & \rightarrow & NO + O \\
O + O_2 + M & \rightarrow & O_3 + M \\
\hline
CO + 2O_2 & \rightarrow & CO_2 + O_3 \quad \text{(net).}
\end{array}$$

Fishman and Crutzen[12] speculate, on the basis of present knowledge about tropospheric photochemistry, that the above mechanism may be the largest source of ozone in the troposphere.

The importance of obtaining a better understanding of the global cycle of CO should not be underestimated. A clearer picture of the distribution of OH in the troposphere as well as a better understanding of the global budgets of methane, tropospheric ozone, and other trace gases will result from a more accurate description of the role of CO. This goal can be realized only as more measurements of ambient atmospheric trace constituents and better laboratory data are made available.

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8. EFFECTS OF CARBON MONOXIDE ON VEGETATION AND SOIL MICROORGANISMS

INTRODUCTION

Because of the potential toxicity of carbon monoxide (CO) to living organisms, there has been much concern over the large quantities (an estimated 103 million metric tons in 1977) of CO released into the atmosphere from anthropogenic sources. While the effects of CO on man and animals have been much studied, relatively little research has been done about its influence on plants. Man's health and well-being, however, are fundamentally and inextricably bound to the success of the plants, which transform the sun's radiant energy into the food and oxygen necessary for habitation of the planet.

The natural global background concentrations of CO, 0.01 to 0.23 mg/m^3 (0.01 to 0.20 ppm),[5] have no known detrimental effects on green plants. In urban areas, however, CO concentrations may be much higher and are closely related to motor traffic density. This relationship means that urban CO concentrations exhibit variation along well-marked diurnal patterns, with peaks corresponding to morning and evening "rush hours." High traffic density, when combined with prolonged periods of air stagnation, has resulted in ambient CO levels of over 34 mg/m^3 (30 ppm) for an 8-hour period in Los Angeles and over 412 mg/m^3 (360 ppm) in London.[5] Even the discovery of these relatively high concentrations, however, has not motivated significant levels of new research into the effects of CO on plants.

Early investigations into CO effects on plant growth and development used high concentration exposures (>11,450 mg/m^3 or 10,000 ppm)[37,38] and were directed at determining the manifestation of external symptoms on treated plants. More recent research has studied effects on vegetation and soils from both ambient and higher concentrations and has been concerned with the following:

1. Visible symptom expression
2. Growth, yield, reproduction
3. Biochemical or physiological response
    a. Photosynthesis
    b. N_2-Fixation
    c. Other metabolic effects
4. Removal of CO from the environment
    a. By plants
    b. By soils
    c. By soil microorganisms
5. Production of CO by photosynthesis

EFFECTS OF CARBON MONOXIDE ON PLANTS

Visible Symptoms

One of the earliest studies on the effect of CO on plants was that of Knight and Crocker in 1913.[19] They exposed pea epicotyls to CO derived from potassium ferrocyanide, from oxalic acid, and from sodium formate in concentrations of 6000 to 24,000 mg/m^3 (5200 to 20,900 ppm). The pea seedlings exhibited reactions including pronounced swelling of the epicotyl, accompanied by stem declination--as much as 90° in some cases. Reactions were similar throughout the range of concentration levels, and no correlation between degree of effect and CO origin was noted.

In 1933, Zimmerman et al.[38] performed a series of experiments in which they observed the reactions of plants exposed to CO. At CO concentrations of 572 to 572,000 mg/m^3 (500 to 500,000 ppm), stem tissues of several plant species exhibited initiation and profuse growth of adventitious roots; stimulated development of latent root primordia also occurred. In a subsequent study,[37] the same authors found that the exposure of plants to 11,000 mg/m^3 (9,600 ppm) CO for up to 23 days also: (1) induced epinasty and hyponasty of leaves; (2) retarded stem elongation; (3) produced smaller and/or deformed leaves; (4) induced premature abscission of leaves, flowers, and fruits; and (5) produced foliar lesions that were characterized by a yellowing of older leaves. Premature leaf abscission was also reported by McMillan and Cope[24] after they exposed seedlings of several geographic variants of Acacia farnesiana to 23,000 mg/m^3 (20,000 ppm) CO for 24-hours. Varying degrees of leaf abscission, including complete defoliation, occurred in the species mentioned, while two other species of Acacia were less severely affected. Garden pea (Pisum sativum) seedlings exposed to 27 mg/m^3 (24 ppm) CO also exhibited increased abscission of older leaves.[6]

Wolf and Kidd[36] found that the greening response of etiolated wheat seedlings upon exposure to light was almost completely inhibited by exposure to CO at levels they describe only as "high concentrations."

Carbon monoxide has found a commercial application in the produce industry. In combination with other gases, it has been used to prolong post-harvest storage and enhance the appearance and consumer acceptability of head lettuce. Stewart and Uota,[32,33] working in the Market Quality and Transportation Laboratory, USDA, held head lettuce in an atmosphere of 34,000 mg/m^3 (30,000 ppm) O_2 plus 17,000 mg/m^3 (15,000 ppm) CO for seven days at 3.3°C. Each head was evaluated for appearance disorders endemic to lettuce, such as butt discoloration, pink rib, and rusty brown discoloration. In general, lettuce held in the experimental atmosphere had a better overall appearance than lettuce exposed to other gas mixtures. Butt discoloration and pink rib were inhibited by exposure to the CO/O_2 combination, while rusty brown discoloration was not affected in any way.

As stated previously, no visible effects have been identified in plants exposed to CO at ambient 0.01 to 0.23 mg/m^3 (0.01 to 0.20 ppm) concentrations.

Growth, Yield, and Reproduction

Concentrations of CO at levels much higher than those found in the ambient air have been shown to inhibit stem elongation in many species of plants. Zimmerman et al.[37] exposed a variety of plant species to CO at concentrations of 115 mg/m^3 to 11,500 mg/m^3 (100 to 10,000 ppm) for from four to 23 days. While practically no growth retardation was noted in plants exposed at the lower level, stem growth was inhibited at the higher concentration by as much as 100 percent when compared with controls. The effects varied considerably among the different species of plants, tobacco being only slightly retarded and others being affected greatly. Exposure to the higher concentration of CO also had a significant effect on the formation and development of new leaves. In many species, new leaves failed to grow as large as normal and had a tendency to curl down at the edge.

Pea and bean seedlings also exhibited abnormal leaf formation after exposure to CO at 27 mg/m^3 (24 ppm) for several days. Pea seedlings showed a decrease in the rate of new leaf development, while leaf formation in bean seedlings was completely inhibited by the eighteenth day. No effect was noted on the relative rates of germination of peas and beans exposed to the experimental atmosphere as compared with controls; likewise, there was no observable difference in the growth rates of exposed plants, as determined by increased stem length.[6]

Several studies have demonstrated the influence of CO on sex differentiation in plants. Minina and Tylkina[25] exposed different varieties of cucumber to CO at concentrations of 1145 mg/m^3 to 11,450 mg/m^3 (1000 to 10,000 ppm) for 50 to 200 hours. Marked shifts in sexual differentiation toward the expression of female characteristics resulted in plants under the influence of the gas. Thus, at the highest level and with prolonged exposure, plants formed exclusively female flowers. With exposure to CO concentrations of 3400 to 5700 mg/m^3 (3000 to 5000 ppm), female flowers developed first, and a very few male flowers a week later. Plants treated at the lowest CO level (1145 mg/m^3; 1000 ppm) proceeded with the development of male flowers, as is normal for the species studied, and then shifted to female expression at the sixth day. Controls developed males first, and continued to do so throughout the course of the experiment.

Similar results were reported by Heslop-Harrison,[10] who studied the modification of sexual expression in Cannabis satova by CO. Young plants exposed briefly to CO at 11,450 mg/m^3 (10,000 ppm) modified the subsequent sexual expression of the dioecious male plants, inducing the formation of intersexual or even functionally female flowers. The effect was registered in flower primordia of a particular age; sex of the older ones was already determined, and younger ones apparently recovered from treatment to develop normally. Basically, the effect of CO in modifying sexual expression is similar to that induced by auxin administration; and it is possible that at effective concentrations the gas upsets auxin metabolism in treated tissues, perhaps by inhibiting enzyme systems normally responsible for regulating endogenous auxin levels. The gross effects of CO on plants are summarized in Table 8-1.

Biochemical and Physiological Processes

Biochemical and physiological responses in plants exposed to CO at above ambient concentrations have been investigated in various species and on different metabolic systems. Results have been conflicting, especially with respect to plant uptake and production of CO. The effects of CO on photosynthesis and nitrogen fixation are discussed below.

TABLE 8-1. EFFECTS OF CO ON PLANTS

Conc.[a]	Duration	Effects	Author
5000		No evidence of swelling in pea epicotyls.	Knight & Crocker[19]
10,000 ppm		Swelling of epicotyls 1-2 cm long; declination of 70-90°.	
20,000 ppm		Swelling of epicotyls 1-1.5 cm long; declination of 80-90°.	
0.05-50% by volume	2-15 days	Stimulated development of root and subsequent root generation. Some alteration of normal geotropic growth pattern.	Zimmerman et al.[38]
0.01-50% by volume	2-30 days	Epinasty, hyponasty, retarded skin elongation, abnormally small new leaf size, general loss of sensitivity to external stimuli, leaf abscission.	Zimmerman et al.[37]
0.3-1.0% by volume	50-200 hrs.	Sex differentiation was shifted markedly towards females.	Minina & Tylkina[25]
1.0% by volume	24-48 hrs.	Generation of female flowers from male plants.	Heslop-Harrison & Heslop-Harrison[10]
1.5% by volume	24 hrs.	Leaf abscission, with severity of effects being dependent upon geographical variant used.	McMillan & Cope[24]
24 ppm	unreported	Exposure of seeds to CO had essentially no effect on germination. Some reduction of leaf formation when seedlings were exposed was noted.	Chakrabarti[6]

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[a] -PPM CO can be converted to mg/m^3 CO by multiplying the above concentrations by 1.145 (@STP).

Photosynthesis--There is evidence that CO can be assimilated by plants. Bidwell and Fraser[4] and Bidwell and Beebe[3] found that many species of plants can absorb and metabolize CO photosynthetically.

Bennett and Hill,[1] however, in 1950, found that CO concentrations as high as 91 mg/m^3 (80 ppm) had essentially no effect on CO_2 uptake in plants. Kortschak and Nickell[18] found that sugar cane leaves removed CO from the atmosphere at a rate of 0.01 mg/m^2/hr.

Nitrogen Fixation--Carbon monoxide has been shown to affect nitrogen fixation. Lind and Wilson[21] demonstrated as early as 1941 that CO inhibition of nitrogen fixation in red clover could usually be observed when plants were exposed to 115 mg/m^3 (100 ppm) CO and that complete inhibition occurred at 573 to 1145 mg/m^3 (500 to 1000 ppm). The authors suggested that the inhibition might be due to carbon monoxide and molecular nitrogen having the same molecular weight, the same number of valence electrons, and many remarkably similar physical properties. Because of these similarities, inhibition of the uptake of atmospheric nitrogen by CO might be the result of the competition of these two gases for adsorption on the surface of the enzyme responsible for fixation. The effect appeared to be readily reversible. The same authors[22] also showed that CO at 23 mg/m^3 (20 ppm) inhibited nitrogen fixation by Azobacter vinelandii, a free-living, nitrogen-fixing bacterium in culture.[24] Table 8-2 summarizes the CO effects on nitrogen fixation.

TABLE 8-2. CARBON MONOXIDE EFFECTS ON NITROGEN FIXATION BY MICRO-ORGANISMS

Conc.[a]	Duration	Effects	Author
.005-0.3%	3-34 days	Inhibition of nitrogen fixation beginning at 0.01% and almost complete inhibition at 0.05-0.1%.	Lind & Wilson[21]
0.05-0.6%	35-45 hrs.	Inhibition of nitrogen fixation observed at 0.1-0.2% with almost complete suppression at 0.5%-0.6%.	Lind & Wilson[22]
PCO of $5+10^2$ Pa	30 min.	50% inhibition of C_2H_2-reducing activity in nitrogen fixing nodules.	Pankhurst & Sprent[27]

[a]-PPM CO can be converted to mg/m^3 CO by multiplying the above concentrations by 1.145 (@STP).

Bergersen and Turner,[2] in 1968, demonstrated that CO inhibition of nitrogen fixation is both specific and competitive with respect to nitrogenase activity. Also, there is an obligatory relationship between the occurrence of leghemoglobin, an oxygen-binding hemeprotein occurring in the nitrogen-fixing root nodules of legumes, and the ability of the nodule to fix nitrogen. Various researchers have demonstrated the great affinity of leghemoglobin for CO.[27,35] Pankhurst and Sprent[27] have shown that this affinity interferes with oxygen binding, thus limiting the amount of oxygen available to the bacteroids (bacteria) in the interior of the nodule and consequently limiting the nitrogen-fixing ability of the bacteria. As further evidence, acetylene-reducing activity, which is used to estimate the rate of nitrogen fixation, was found to be inhibited by CO in soy bean nodules.

REMOVAL OF CARBON MONOXIDE FROM THE ENVIRONMENT

Many people are concerned about the large amounts of CO being released into the atmosphere by both anthropogenic and natural sources, fearing that ambient global CO concentrations may someday increase to levels detrimental to plants. Large amounts of CO are emitted annually to the atmosphere from man's activities; however, as of 1973, ambient concentrations did not appear to have changed appreciably over the previous 20 years.[16] It is apparent, then, that something happens to CO soon after its liberation. The chemical and photochemical reactions known to transform CO in the atmosphere were for years regarded as being too slow to account for the disappearance of the quantity of CO in question. Consequently, investigative attention was turned to components of the biosphere as possible utilizers of CO.[10] The utilization of CO by plants and soil microorganisms is considered in the following sections.

Plants

As previously mentioned, it has been demonstrated that CO can be assimilated by plants.[3,4] Bidwell and Fraser[4] supplied ^{14}CO to bean leaves in light or darkness at 174 to 314 mg/m^3 (150 to 270 ppm) in air. In the presence of light, CO was absorbed and converted mainly to sucrose and proteins. In darkness, ^{14}CO was absorbed nearly as fast as in light, but was almost completely converted to CO_2 and released.

Carbon monoxide fixation by a number of plant species under light was measured during exposures of 0.87 to 8.7 mg/m^3 (0.75 to 7.5 ppm) in air, with rates varying from 0 to 0.25 μmole/dm^2/hr. Rates were roughly proportional to CO concentration but were unrelated to rates of photosynthesis. Bidwell and Fraser[4], using the bean leaf as an intermediate CO absorber, at 1.7 mg/m^3 (1.5 ppm) CO with an uptake rate of 0.06 μmole/dm^2/hr, and assuming a leaf area index (area of leaf per unit area of ground) between three and 30, calculated that the rate of CO uptake would be 0.5 to 5 mg/m^2 of ground per hour, or about 12 to 120 kg/km^2 per day.

Kortschak and Nickell[18] found that the leaves of the sugar cane plant can absorb and metabolize CO, with sucrose as an end product. These authors, however, found the rates of CO uptake to be on the order of 10^{-4} mg/dm^2/hr, which would be too low to be significant in removing CO from the atmosphere. Hill,[11] in 1971, and Hill and Chamberlain,[13] in 1976, found that under carefully controlled laboratory conditions, alfalfa canopies did not significantly remove CO from the atmosphere. The production and utilization of CO by plant life is summarized in Table 8-3.

TABLE 8-3. PRODUCTION AND UTILIZATION OF CO BY PLANTS AND MICRO-ORGANISMS

Conc.[a]	Duration	Effects	Author
Wide variation in data for different plants and experimental conditions.		Data suggests significant role for plants in reducing atmospheric CO concentrations; production of CO may exceed uptake, however.	Delwiche[9]
0-10 ppm	1-2 hr.	The amount of CO uptake by alfalfa was below limits of detection.	Hill[11]
100-120 ppm	3 hrs.	Indigenous soil fungi reduced atmospheric CO concentration from 100-120 ppm to 0 in 3 hrs.	Inman & Ingersoll[16]
200-360 ppm	15-25 min.	Test plants absorbed CO, converting it to organic material by day and CO_2 by night.	Bidwell & Fraser[4]
		It is indicated that algae are responsible for significant natural CO emissions.	Crespi & Katz[7]
80% CO in air.	30 days	Decrease in CO content.	Nozhevnikova & Zavarzin[26]
6 ppm	15-45 min.	Exposed plants absorbed CO at an average rate of 0.19/µl/hg fresh weight.	Bidwell & Beebe[3]
Not reported	Not reported	CO incorporation rates varied from 0.32 n moles/dm^2-hr to 28.48 n moles/dm^2-hr. Grasses tended to have the lowest rate of fixation.	Shaedle & Oliver[29]
<0.1-0.6 ppm	24 hrs.	Air CO within closed box. Diurnal variation, temperature-dependent. Glass box over natural soil surface.	Seiler[30]
		Several micro-organisms produce trace amounts of CO in the range of 0.4-2.6 ppm. Media containing glucose was found to stimulate CO production.	Radler et al.[28]

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[a] PPM CO can be converted to mg/m^3 CO by multiplying the above concentrations by 1.145 (@STP).

Soil Microorganisms

Inman and Ingersol[16] and Inman et al.[17] tested non-sterile potting soil in plastic atmospheric chambers and found that CO concentrations dropped from 105 mg/m^3 (90 ppm) to 0 within a 3-hour period. No change occurred in CO concentrations over the controls using sterile soil. This indicated that potting soil, at least, had a distinct capacity for CO uptake. Samples of natural soils, when tested comparatively, all varied in their ability to take up CO. Carbon monoxide uptake appeared to be correlated with high organic matter and low pH.

From the various tests conducted, it appeared that the capacity for CO uptake was mediated either by a biological mechanism, or by some physical absorptive process which, on the basis of the inactivity of sterile soil, was labile to steam heat. A series of tests was conducted to characterize the phenomenon further. The authors found that when 2.8 kg of autoclaved potting soil was inoculated with 1 g of non-sterile potting soil, uptake activity increased as a function of time following the inoculations. Uptake of CO was inhibited by the addition of 50 ml of 10 percent NaCl to 200 g potting soil. Incubation under anaerobic conditions for five days prior to testing also inhibited CO uptake, as did drenching the soil with 50 ml of an antibiotic solution containing streptomycin, erythromycin, and cyclohexamide.

These results strongly indicated that the uptake of CO was mediated by a biological rather than a physical mechanism. It was suspected that certain elements of the soil microflora were responsible for CO fixation. Inman and Ingersoll[16] then attempted to estimate the total capacity of the soil to remove CO from the atmosphere. The average activity of the soils tested was 8.44 mg of CO/hr/m^2 of soil, equivalent to 191.1 metric tons per year per square mile. If it is assumed that this value is representative of the average capacity of soils in the temperate zone, the capacity of the total soil surface of the Continental United States to take up CO [2,977,128 $miles^2$ (7,792,533 km^2)] is estimated to be 569 million metric tons per year.

Liebl and Seiler[20] found soil uptake of CO to be not so great as that reported by Inman and Ingersoll,[17] but concurred that the soil must be recognized as a major natural sink for CO released into the atmosphere. Microorganisms other than the soil microflora may have a role in atmospheric CO removal. Uffen[34] described a species of Rhodopseudomonas, a species of photosynthetic bacteria that requires CO as the sole source of carbon and uses it under anaerobic conditions. Also, Nozhevnikova and Zavarzin[26] have stated that there are bacteria that have the capability of oxidizing CO and that are capable of growing and developing on a substrate in which CO serves as the sole source of carbon and energy. These bacteria represent a potentially powerful factor in eliminating CO from the atmosphere. The bacteria that oxidize CO to CO_2 have not been well studied. Table 8-4 summarizes data showing soils as CO sinks.

TABLE 8-4. SOILS AS A SINK FOR CARBON MONOXIDE

Conc.[a]	Duration	Effects	Author
80-130 ppm in air	2-19 hrs.	Results indicated that the phenomenon of CO uptake by soil was due to a biological rather than physical mechanism and that CO uptake was due primarily to indigenous soil microflora. Rate of uptake was also temperature dependent.	Ingersoll[14]
5-100 ppm in air	2 hrs.- 45 days	The uptake of CO by soils *in situ* is variable with soils ranging from 7.5 to 104.0 mg CO/hr/m^2. Tropical soils were most active; desert soils were least active. CO uptake by soils was greatest at a concentration of 100 ppm and decreased as the concentration decreased.	Ingersoll[13]
0-40 ppm in gas	Not reported	Removal of CO by the forest soil exceeded that of the field soil at all moisture contents when the two were compared at the same CO concentration. Maximum rates of removal approached 0.20 mg CO/dm^2 hour.	Heichel[9]
100 ppm	2-3 hrs.	Soils of major vegetative regions of North American were tested as well as roadside soils and soils under cultivation. CO uptake ranged from 7.6-115 mg CO/h/m^2 with tropical soils showing greatest activity and desert soils the least. Roadside soils were consistently higher in CO uptake capacity. Natural soils were more active in CO uptake than sterile soil.	Ingersoll, Inman, & Fisher[15]

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[a] PPM CO can be converted to mg/m^3 CO by multiplying the above concentrations by 1.145 (@STP).

PRODUCTION OF CARBON MONOXIDE BY PLANTS

Carbon monoxide evolution by fresh water algae has been shown by Crespi and Katz[8] to be associated with biosynthesis and degradation of photosynthetic pigments. Their results indicated that plants may be the source of 10^8 tons or more of CO per year. Production and utilization of CO by algae and two higher plants (Zostera marina and Medicago sativa) have been reported by Loewus and Delwiche.[23] The assimilation and utilization of CO by a variety of plants proceeds at a significant rate, exceeding maximum observed rates of production in some cases. From laboratory studies, it can be calculated that a field of 100 hectares of alfalfa could produce approximately 2000 liters of CO in a 10-hour period. The effect of temperature on the soil evolution of CO also still remains to be learned, although there are data on temperature effects of CO uptake by soil.[15] Carbon monoxide production rates were found, however, to be light-dependent with an average value of 3×10^{-13} g/cm^2/sec of leaf area for a radiation intensity of 5×10^4 ergs/cm^{2}sec. The total CO production by plants is estimated to be 0.5 to 1.0 x 10^{14} g/year.[31] This estimate indicates that plants may contribute significantly to the atmospheric CO cycle, with production rates comparable to the total CO production rate in the oceans.

SUMMARY

Of the literature dealing with effects of CO on microorganisms and plants or with the production and utilization of CO by them, most earlier work was directed toward physiological studies without reference to atmospheric concentrations. There are few studies from which thresholds of detrimental (or other) effects might be inferred. Thus, although neither defoliation nor the inhibition of leaf formation is demonstrable at concentrations of 11,000 mg/m^3 (10,000 ppm) CO or higher, the studies described in this chapter provide little information regarding possible threshold effects since the concentration used was more than 10,000 times greater than normal atmospheric levels.

The few reports of effects at lower concentrations suggest that influences in the normal atmospheric concentration range for CO are not great and that a "threshold" as such does not exist. Since plants can both metabolize CO (apparently photosynthetically) and produce CO, it is considered a normal constituent of the plant environment.

Microorganisms have a wide range of responses to CO, including oxidizing it autotrophically. Thus, any change in atmospheric concentration could be expected to result in a corresponding alteration of soil microbial population distribution; however, no studies seem to have been made. This flexibility in the response of the soil microflora to changing environmental conditions is a generalized one, and soil can be viewed as a buffering system and eventual sink for CO.

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9. METABOLISM OF CARBON MONOXIDE IN MAMMALS

Adverse health effects of carbon monoxide (CO) are due primarily to diminished oxygen (O_2) transport by the blood and to interference with biochemical utilization of O_2 in tissues. The chemical binding of CO to hemoglobin (Hb) and other heme compounds in tissues is so much stronger than the binding of O_2 to these compounds that O_2 is excluded in part from its normal physiological role. The apparent toxicity of CO is related to the strength of the coordination bond formed with the iron atom in protoheme ($C_{34}H_{32}N_4O_4Fe$). Hemoglobin, a ferrous iron complex of a protoporphyrin combined with globin, is contained within the erythrocyte (red cell). A small amount of CO is produced within the body by normal breakdown processes, which result in carboxyhemoglobin (COHb) levels of about 0.5 percent in blood. Any increase above this level is assumed to result from outside sources. The excretion of CO through respiration appears to occur in two stages, rapidly at first and then more slowly.

INTRODUCTION

Mammals obtain CO from two sources: (a) endogenously, normally from the breakdown of Hb, and (b) exogenously, by inhaling CO from the ambient air. The quantity of endogenous CO is small, although greater quantities can be produced in various disease states and by ingestion or inhalation of certain drugs and chemicals. Exogenous CO, from inhalation, increases the concentration of CO in the alveoli of the lung, which in turn increases its diffusion through the pulmonary and capillary membranes into the blood. The final and most important factor is the great avidity with which the Hb in the red cell (erythrocyte) combines with CO. The changes in concentration of this combined Hb and CO (COHb) are finally determined by many factors: the endogenous CO produced, the concentration of CO inhaled, the volume of inhaled air (which is related to the degree of physical activity of the individual), body size, barometric pressure, and the functional capacity of the lung itself. These factors have been briefly summarized by Klocke[35] and Coburn.[10]

An O_2 supply adequate to maintain tissue metabolism is provided by the integrated functioning of the respiratory and cardiovascular systems to transport O_2 from the ambient air to the various tissues of the body. Nearly all of the O_2, except that dissolved in plasma, is bound reversibly to the Hb contained within the erythrocytes. The most significant chemical characteristic of the air pollutant, CO, is that it is also reversibly bound by Hb. Therefore, it is a competitor with O_2 for the four binding sites on the Hb molecule. The reduction in the O_2-carrying capacity of the blood is proportional to the amount of COHb present. A simple example is provided by comparing an anemic individual having 7.5 g percent of Hb with another individual having 15 g percent but with half of this Hb as COHb, i.e., 50 percent COHb. The O_2-carrying capacity is equivalent in both. However, the amount of available O_2 is still further reduced by the inhibitory influence of COHb on the dissociation of any oxyhemoglobin (O_2Hb) still available.

THEORETICAL CONSIDERATIONS

The equilibrium constant, M (Haldane's constant), expresses the relative affinity of Hb for CO and O_2 under conditions in which the concentration of reduced Hb is minimal. This M[21] is defined by the following equation:

$$\frac{(COHb)}{(O_2Hb)} = M \frac{P_{CO}}{P_{O^2}}$$

where P_{CO} and P_{O^2} represent the equilibrium gas partial pressures: each pressure being the same in the erythrocytes or Hb solution as in the equilibrated gas phase; (COHb) and (O_2Hb), on the left side of the equation, are the concentrations of COHb and O_2Hb, respectively. The value of M is about 200 plus in most mammalian species (246 in man), in spite of the fact that CO combines with Hb more slowly than does O_2. Carboxyhemoglobin dissociates very slowly because of the tight binding of CO to Hb. Technically, it is not possible to measure the rate of dissociation of CO from partly saturated Hb. The dissociation velocity constant has been measured only by a few investigators on sheep and human Hb fully saturated with CO. The most commonly used values for M in the recent literature have ranged from 210 to 230. Roughton[56] has presented the most comprehensive analysis of the interaction of CO with erythrocyte Hb. He reviewed the extensive early literature and presented new data on several portions of the dissociation curve. Roughton's data clearly indicate that a mean value for M is approximately 246, although it is different for various portions of the dissociation curve. The attraction by the Hb molecule for CO, compared to that for O_2, is thus suggested to be some 246 times greater. In fact, this value was the one originally suggested by Douglas et al.[21] and confirmed by Joels and Pugh.[34]

Solution of Haldane's equation would give an approximate level of COHb; e.g., exposure to ambient environments containing 29, 57, or 114 mg/m^3 (25, 50, or 99 ppm) CO would lead to COHb saturations of approximately 4.8, 9.2, and 16.3 percent if arterial O_2 pressure were 80 torr. The CO enters the lungs with each breath and diffuses across the alveolar-capillary membrane in a manner similar to O_2. If air with a constant concentration of CO is breathed for hours, the rate of uptake of CO decreases exponentially (roughly so) until an equilibrium state is attained in which the partial pressure of CO in the pulmonary capillary blood is equivalent to that in alveolar air. The half-time for this process is approximately 2 hours in a healthy individual engaged in light physical activity.[6] This process is altered during heavier physical exercise or in certain disease states.

Transport of O_2 in the blood is best described by the O_2Hb dissociation curve (Figure 9-1). This curve, in the presence of COHb, is no longer classically sigmoid but is shifted to the left so that a lower O_2 pressure is present for the same O_2Hb saturation compared to blood with COHb[57] (see Figure 9-2). Roughton and Darling[57] pointed out that only the upper half of the steep portion of the O_2 dissociation curve was operative for O_2 unloading, with the lower portion serving as a reserve. When COHb is below 40 percent, O_2 uptake is maintained by use of some or even all of the reserve O_2 from undissociated O_2Hb at low tensions.

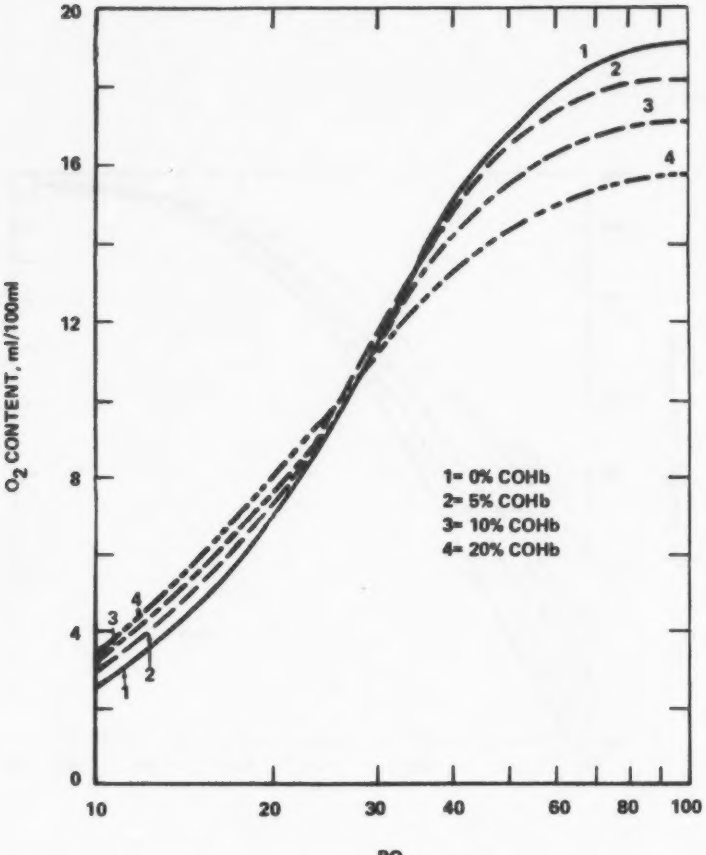

Figure 9-1. Oxygen dissociation curve with and without the presence of varying concentrations of CO.

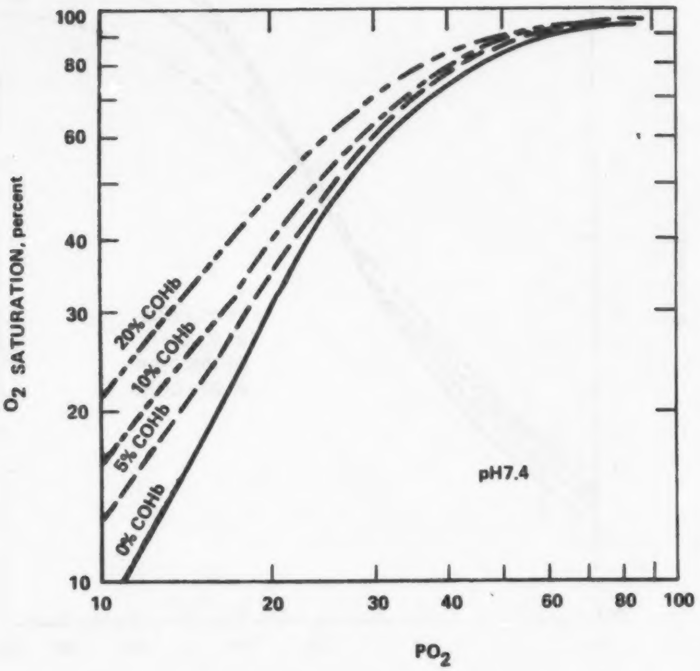

Figure 9-2. Blood oxygen dissociation curves at various COHb values.[57]

If COHb exceeds 40 percent, adequate amounts of O_2 cannot be delivered to the tissues. Figure 9-2 illustrates the extent of the Haldane shift to the left more clearly than the classical curves of Figure 9-1. Mulhausen et al.[42] illustrate this shift by observing that the P_{50} (half saturation) O_2 tension shifted from 26.7 to 23.2 torr in their subjects, who were intermittently exposed to high concentrations of ambient CO. Ledwith[36] and Collier[16] have presented methods for determining P_{50} in the presence of COHb and have extended theoretical considerations for the computation of P_{O_2} in the presence of CO. Carbon monoxide not only diminishes the total amount of O_2 available by direct replacement of O_2 (Figure 9-1), but also alters the dissociation of the remaining O_2 so that it is held more tenaciously by Hb and released at lower O_2 tensions. The O_2Hb curve in the presence of COHb progressively resembles the simple O_2 dissociation curve of myoglobin. Myoglobin is a heme compound with only one heme unit per molecule and does not exhibit heme-heme interactions. It is possible that the combination of one or more of the four heme groups in Hb with CO decreases the heme-heme interactions of the remaining heme units and results in a molecule approaching the behavior of myoglobin. Hlastala et al.[32] have presented data indicating that heme-heme interaction is different for O_2 than for CO. This decreased heme-heme interaction has been confirmed by Okada et al.[44]

Carbon monoxide poisoning is similar to anemia wherein the O_2 capacity of the blood is reduced because the Hb concentration is reduced. The O_2 dissociation curve of blood obtained from patients with anemia is shaped like the normal curve except that it is vertically compressed. However, when curves from individuals with a 50 percent reduction in Hb content are compared to dissociation curves determined in the presence of 50 percent COHb, there are striking differences. Consequently, the tendency to make such comparisons is likely to lead to erroneous deductions as to effects occurring at the tissue level. Brody and Coburn[5] have discussed these differences in relation to arterial and venous P_{CO} and P_{O_2} levels.

The possibility that an adaptation to CO (such as in the case of adaptation to high altitudes) could alter the position of the O_2 dissociation curve as a consequence of extensive exposure to CO appears to have been answered. Mulhausen et al.[42] found no change in the degree of left shift in the blood of individuals exposed to CO for a period of eight days. Unfortunately, the average COHb of 13 percent was based on large individual variation in COHb and periodic exposure to relatively higher inhaled CO concentrations.

Several investigators have sought for evidence of a potential shift of the curve back to the right. Red cell 2,3-diphosphoglycerate is increased in individuals with anemia and in individuals residing at high altitudes. 2,3-Diphosphoglycerate (2,3-DPG) is a phosphorylated by-product of glycolysis. In erythrocytes of man and most other mammals, the molar concentration of 2,3-DPG is roughly equal to that of Hb. It and some other organic phosphates are bound rather strongly to deoxyhemoglobin (de-O_2Hb) but have little affinity for O_2Hb. Increases in 2,3-DPG shift the effective O_2 affinity; i.e., a shift of the O_2Hb dissociation curve to the right occurs. Astrup[3] found a small decrease in erythrocyte 2,3-DPG in human subjects maintained with 20 percent COHb for 24-hours. Dinman et al.[20] conversely found a small increase in 2,3-DPG in human subjects after three hours at approximately 20 percent COHb and in rats exposed to higher but variable concentrations of CO. A shift of the dissociation curve does not appear to indicate an important adaptation to CO exposures of less than a few days. Cameron et al.[6] have reported that CO has a significantly greater effect upon the position of the O_2 dissociation curve in patients with sickle-cell anemia than in normal subjects. It is possible that in sickle-cell anemia there is an increased Hb affinity for CO.

Any consideration of the toxicity of CO must include not only the decrease in the O_2-carrying capacity of Hb but also the interference with O_2 release at the tissue level. Ayres et al.[4] raised the COHb concentration to an acute average of 9.0 percent saturation in 26 subjects, some with and some without heart disease. Mixed venous P_{O2} decreased from 39 to 31 torr, suggesting a decrease in tissue O_2 pressure since mixed venous O_2 pressure must represent, at least roughly, the maximum values for tissue oxygenation. Arterial O_2 tension decreased five torr from the control level of 81. Ayres et al.[4] also measured the alveolar-arterial O_2 gradient. The nine torr increase in the gradient implies that the pulmonary arterio-venous shunts became larger, accounting for both the increased alveolar-arterial O_2 difference and the decrease in arterial O_2 tension. Power,[52] however, found that CO diffuses more rapidly through blood and pulmonary and placental tissues than would be predicted from comparative solubilities of O_2 and CO in water. Brody and Coburn[5] have indicated that if the O_2 content of the mixed venous blood is abnormally low, as in anemia or CO poisoning, the effect of the shunted blood in lowering arterial P_{O2} will be greater than normal, and a small increase in the alveolar-arterial pressure difference ($A\text{-}aD_{O2}$) will result. The change in the shape of the O_2Hb curve due to the presence of CO will also increase $A\text{-}aD_{O2}$. Furthermore, Brody and Coburn[5] showed that mild increases in COHb concentrations would have little or no influence on the $A\text{-}aD_{O2}$ in normal subjects. However, in patients with large intracardiac right-to-left shunts or with chronic lung disease and regional variation in the ventilation perfusion ratio ($\dot{V}_A/\dot{Q}$), the presence of CO in the blood will increase the $A\text{-}aD_{O2}$.

The venous P_{O2} values expected to result from various COHb levels can be calculated.[24,49] If blood flow and metabolic rate remain constant, equilibration with an ambient CO of 200 ppm (25 percent COHb) will lower venous P_{O2} from 40 to less than 30 torr. A similar degree of venous hypoxemia results from an ascent by a normal individual to an altitude of 3658 m or from a 35 percent reduction in O_2 capacity in an anemic patient. It can also be calculated that at 5 percent COHb, there will be only a slight drop in the mixed venous P_{O2}. Even more significant relationships can be obtained by plotting O_2 content against the partial pressure of O_2.[57] The difference in O_2 content at various percentages of COHb from zero to 20 reveal that only a small change occurs in the availability of O_2 due to the Haldane effect (Figure 9-1). It was this evaluation that led Roughton and Darling[57] to conclude that COHb concentrations lower than 40 percent produce relatively easily compensated restrictions in the amount of O_2 available for tissue delivery. This can only be applied to subjects with normal respiratory and circulatory systems. The small reductions in O_2 content at 5 to 10 percent COHb may be quite critical for patients suffering from cardiovascular diseases or chronic obstructive lung disease. Coburn et al.[12] published a detailed theoretical analysis of the physiology and variables that determine blood COHb levels in man. The details of the formulas used in these calculations are presented in the following section. Permutt and Fahri[49] have calculated that when COHb levels are approximately 5 percent, resting coronary blood flow (CBF) must increase about 20 percent in order to prevent myocardial ischemia. This theoretical calculation has been confirmed experimentally by Adams et al.[1] and Horvath,[33] who demonstrated such approximate increases in CBF despite having used very different methods to increase blood COHb levels.

Cerebral function is said to be altered at low COHb levels, and it is of some interest to examine the available data on cerebral P_{O_2} tensions, cerebral blood flow, and cerebral metabolism. Zorn[63] used platinum electrodes to study the effects of CO inhalation in vivo on brain and liver P_{O_2}. Tissue P_{O_2} fell in both organs, even at COHb concentrations of 2 percent, and the fall was approximately linear to increases in COHb. Oxygen partial pressure decreased 0.2 to 1.8 torr for each 1 percent fall in O_2Hb saturation. These data suggested that CO had influences other than at the intracellular level, since if it was limited to this area, tissue P_{O_2} would have been expected to increase. Weiss and Cohen[62] performed similar studies on rat brain and muscle. They found a decrease in cerebral cortical P_{O_2} consequent to inhalation of low levels of CO. Unfortunately, they did not measure COHb levels in these rats, although, in a group of sham-operated animals exposed to similar levels of inhaled CO, COHb had increased to 3.3 percent. Haggendal et al.[31] reported that, during progressive CO administration to dogs, cerebral blood flow did not increase until COHb levels attained 20 percent. Thereafter, cerebral blood flow increased progressively and was double the control values when COHb reached 50 percent. Paulson et al.[48] measured cerebral blood flow in five human subjects. No changes were observed at 8 percent COHb, but a greater than 20 percent increase occurred when COHb was 20 percent. Despite the increase in cerebral blood flow, the P_{O_2} of jugular venous blood was reduced by 3.4 torr at this high level of COHb. Jugular venous P_{O_2} was reduced one mm when COHb was 8 percent, but no note was made as to whether this was a significant decline. Arterial and jugular venous lactates were said to be unchanged.

McGrath and Martin[39] have presented evidence that CO may have a direct effect on the heart in addition to its well known Hb-mediated effect. Carbon monoxide caused a reduction in developed tension and an increase in resting tension of cardiac muscle. Recovery of muscle function was also depressed. Chen and McGrath[7] have also reported that CO has a specific effect on the myocardial conducting system. Carbon monoxide may have specific effects independent of the reduction in O_2 availability.

Total-body asanguineous, hypothermic perfusion was recently suggested as a therapeutic measure in CO poisoning.[2] In an attempt to explain this beneficial effect, Ramirez et al.[53]

compared the survival of normal dogs given high levels of CO versus acutely anemic dogs transfused with COHb blood. All normal dogs with COHb levels of 54 to 100 percent died within 0.25 to 10-hours but the transfused animals, having a final mean COHb of 80 percent after transfusion, survived. The authors suggested that hypoxic anemia was not the principal mechanism of CO toxicity, but that the blocking out of the energy supply on the cellular level governed by the cytochrome system was heavily involved.

Goldbaum and co-workers[26-29] have suggested that, in order for CO to affect mitochondrial respiration (particularly through combination with cytochromes), it must be dissolved first in plasma. They report that if 0.001 ml CO is physically dissolved in the plasma, even though COHb levels were above 20 percent, this physically dissolved CO combines with the cytochromes, and it is this combination rather than the reduction in O_2-transport capacity of the blood that appears to be responsible for the toxic effects of CO. Dogs injected with CO intraperitoneally survived indefinitely, even though their COHb levels were as high as 75 percent. Orellano et al.[45] presented experimental data that suggested that CO injected intraperitoneally into dogs is nontoxic. The implication of these results is that the CO tension in the blood after CO inhalation is high because the combination of CO with Hb is not instantaneous. They postulated that blood leaving the lungs has a high CO tension, and this physically dissolved CO is more likely to combine with the various heme compounds in tissue and so produce a local effect on mitochondrial metabolism. There may be some questions regarding these observations since the kinetics of CO transport would not be completely supportive of the changes observed. Drabkin et al.[22] had reported a similar effect in 1943 and explained the lack of toxicity as the Haldane effect.

Chiodi et al.[8] indicated that the respiratory center or arterial chemoreceptors were not stimulated to elevate the respiratory minute volume even when COHb levels were as high as 40 percent. Mills and Edwards[41] measured the frequency of electrical impulses in the afferent nerves from the aortic and carotid chemoreceptors. They showed that CO administration does result in chemoreceptor stimulation. The response appeared to be approximately linear with the COHb concentration (at least definitely above 8 percent). These findings suggest that CO may stimulate breathing. The failure to observe an increased minute volume might be explained by considering that, in the presence of CO, the chemoreceptor stimulation was offset by hypoxic depression of brain structures that are involved in breathing. There is some evidence that this balancing between chemoreceptors and central nervous depression is operative in anemia.[58] The difference in observed responses may be related to varying sensitivities of the baro- and chemoreceptors to carbon monoxide and to P_{O2}. Additional investigations are needed to clarify this physiological effect of CO inhalation.

ABSORPTION, EXCRETION, AND EQUILIBRATION

Carbon monoxide in the body is produced endogenously from the catabolism of the pyrrole rings originating from Hb, myoglobin, cytochromes, and other heme-containing pigments. The adult's endogenous production normally amounts to approximately 0.4 ml (STPD) per hour.[10,14]

Increased production can occur in hemolytic anemias,[15] during the menstrual cycle in females,[18] and in the induction of liver cytochromes consequent to administration of drugs such as phenobarbital or diphenylhydantoin.[9] The basal production of endogenous CO, approximately 0.31 ±0.07 μmole/(hr/kg), can be increased threefold in these conditions.[10] These increases are of minimum importance in the elevation of COHb compared to the increases that occur from exogenous CO input. Mercke et al.[40] have found diurnal endogenous production to be lowest in the morning. Fasting for 24 hours resulted in increased endogenous production. It should be kept in mind that there is considerable inter- and intra-individual variation in endogenous CO production. The primary factors determining the final level of COHb are inspired CO, minute alveolar ventilation in rest and exercise, endogenous CO production, blood volume, barometric pressure, and the relative diffusion capability of the lungs. The rate of diffusion from the alveoli and the concomitant combination of CO with the blood Hb is the step limiting the rate of uptake into the blood. A special case of CO exposure, important to a large proportion of the population, is the intake from tobacco smoking. This is a direct exposure for the smoker and an indirect exposure for the non-smoker.[12]

The classical CO absorption curves of Forbes et al.[23] have been reevaluated for the resting person[50] and are presented in Figure 9-3. Peterson and Stewart[50] exposed human volunteers to a variety of different CO concentrations for periods ranging from 0.5 to 24-hours. Using regression analysis, they derived the following empirical relationship for blood COHb as a function of ambient CO concentration and exposure time:

$$\mathrm{Log}_{10}\, y = (0.85733 \log_{10} x + 0.62995 \log_{10} t) - 2.29519;$$

where y = percent COHb,

x = CO concentration in ppm, and

t = time in minutes.

Although these new data come closer to presenting potential uptake in individuals exposed to present-day ambient concentrations of CO, they do not address themselves to the uptake that would occur in an active individual. Ott and Mage[46] have objected to the Peterson and Stewart presentation because it is a static model. They indicate that the use of averaging periods as long as one hour versus periods of 10 to 15 minutes introduces an error into recorded urban concentrations by obscuring short-term high concentrations.

The data presented by Forbes et al.[23] have until recently been the only experimental information available that takes ventilation into account and, even so, their information is inadequate since the full range of inspired, ventilatory volumes possible in exercising man were not considered. Peterson and Stewart[50] reported excellent correlation between the COHb values measured in their volunteer subjects with those predicted by the Coburn et al. equation[12] (see Figure 9-3), which permits the calculation of blood COHb[50] as a function of time, considering appropriate physiological and physical factors. This equation was used to calculate COHb concentrations for exercising individuals, as represented in Figure 9-4. In

ABSORPTION OF CARBON MONOXIDE

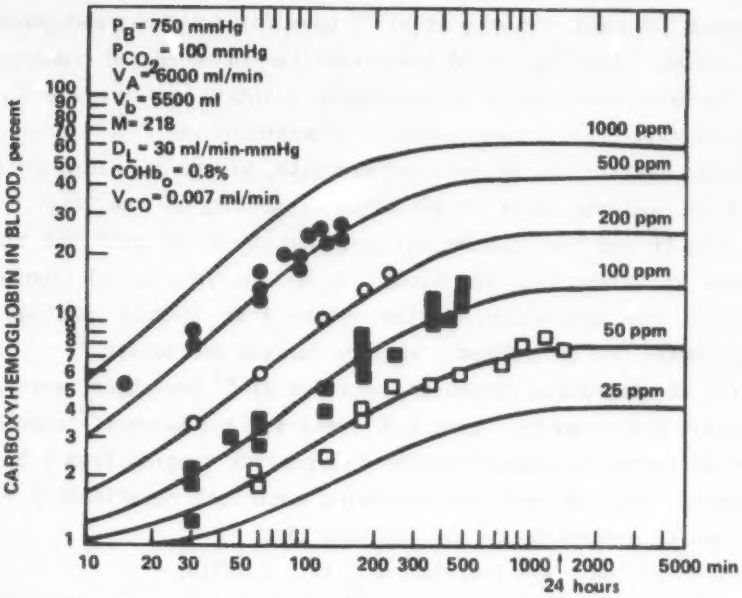

Figure 9-3. Exposure duration, ambient carbon monoxide concentrations (resting individuals). (Reprinted from Annual Review of Pharmacology, with the permission of the publisher.)

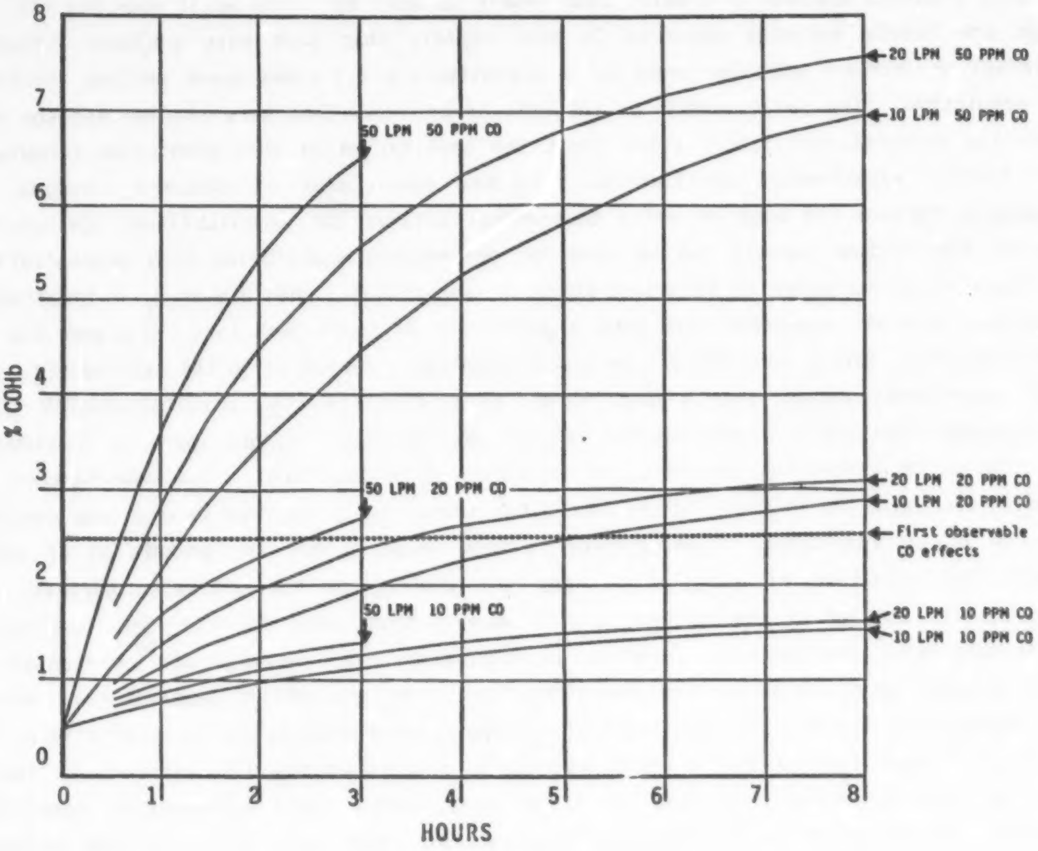

Figure 9-4. Exposure duration, ambient carbon monoxide concentrations. (Exercising individuals)

the equation, O_2Hb concentration depends upon COHb in a complex way and, therefore, solution of the equation requires some special computer techniques with a second approximation. These have been attempted, and general solutions are available.[12] Peterson and Stewart[51] have shown that this equation appears to predict COHb levels as well for women as it does for men, even though the female subjects absorbed CO more rapidly than most male subjects. Exercise sufficient to increase alveolar ventilation approximately 2.5 times above resting levels was also predictive. The small number of subjects of each sex that were studied and the relatively low exercise ventilatory rates limit the application of this prediction formula and await further experimental verification. Further development of Coburn's concepts will undoubtedly improve the base on which theoretical uptakes can be calculated. Calculations based on the Haldane formula can be used for determining equilibrium COHb concentrations.

There is no excretion of CO unless there is respiration. When air or O_2 is breathed, CO dissociates from Hb, myoglobin, and heme pigments and diffuses back into the plasma and into the expired air. Carbon monoxide can be almost completely recovered in the expired air. Some animal experiments suggest that a small amount is oxidized in vivo to carbon dioxide (CO_2).

Adequate data are available on the rate of absorption of CO, but there is considerably less information concerning the rates of CO egress from the lungs. The same factors that determine how much CO is taken up by the blood should apply in reverse when one considers clearance of CO from blood. The primary factors involved are the amounts of CO and O_2 present, the magnitude of ventilation, and the quality of the diffusion barrier. Age influences the quality of the barrier, and it appears that, with advancing age, the barrier becomes more dense and there are fewer gas exchange membranes. Sedov et al.[59] presented data on the elimination of CO at various atmospheric pressures and ambient temperatures. Neither lower barometric pressures nor high temperatures appreciably altered the rates of elimination. Pace et al.[47] have implied that a sex difference in elimination may also exist--i.e., females appear to have a faster rate than males, at least under their experimental conditions. Similarly, Goldsmith et al.[30] indicated that men and women have different COHb excretion rates--men having a half-life of 4-hours and women, 3-hours. They explained these differences as being related to physiologic differences in blood volume and pulmonary vital capacity.

Available evidence suggests the presence of a biphasic decline in the percentage of COHb in arterial blood.[25,61] There is a rapid, initial, exponential decline (distribution phase), probably related to distribution of CO from the circulating blood to splenic blood, myoglobin, and cytochrome enzymes. Elimination of CO via the lungs also occurs during this phase. The distribution phase, which persists for the first 20 to 30 minutes, is followed by a slower linear decline (elimination phase). This phase probably reflects the rates of release of CO from Hb and myoglobin, pulmonary diffusion, and ventilation, as well as the fact that P_{CO} decreases with time. Myrhe[43] found a similar biphasic excretion pattern to occur at an altitude of 1630 meters. However, he noted that the half-life of COHb was much longer--5.5-hours. Tiunov and Kustov[60] found that, following continuous exposure to CO for 49 hours, 50 percent was eliminated in 30 to 180 minutes and 90 percent within 180 to 420 minutes. Other investigators[12,40] have reported exponential COHb elimination curves over many hours. However, they were unable, because of inadequate sampling in the early phase of elimination, to observe the more rapid initial decline. The absolute level of COHb at the beginning of elimination studies apparently modifies the rate of disappearance of CO from the blood. Utilizing the simpler linear relationship, it appears that half-times for COHb levels of 5 to 16 percent and 20 to 43 percent are approximately 190 and 134 minutes, respectively. If the more accurate exponential (semilogarithmic) relationship is used, the half-times for the above levels of COHb are 226 and 148 minutes, respectively. These rates must be considered approximations, since considerable individual variability has been observed. In summary, discharge of CO occurs first at a rapid rate and then becomes slower with time; and the lower the initial level of COHb, the slower the rate of disappearance. Apparently, no studies have been made to determine the disappearance rates at the low levels of COHb (2 to 4 percent) that might be present following exposure to ambient concentrations of CO.[19]

Several procedures have been tried that could accelerate the excretion of CO from the blood of individuals who have high levels of COHb (40 to 70 percent). Pace et al.[47] reported that treatment of such individuals in a recompression chamber with an O_2 level equivalent to 2.5 atmospheres (partial pressure of O_2 equal to 1900 torr or an alveolar O_2 pressure of 1801) would facilitate removal of CO. They indicated that one hour in such a chamber would result in the reduction of COHb to 10 to 15 percent, whatever the initial level might have been. Malorny et al.[38] have revived the Henderson and Haggard treatment concept. They evaluated the influence of breathing different gas mixtures on the excretion of CO in animals having high COHb levels (60 to 74 percent). It was determined that in animals, 50 percent could be excreted in 19 minutes if 5 percent CO_2 and 95 percent O_2 were breathed, compared to 28 minutes for 100 percent O_2, and 41 minutes for ambient air. Another approach was suggested by Agostini et al.[2] who employed a total-body asanguineous, hypothermic procedure. The biological half-life of CO in man under normal conditions is one and one-half hours. This approach to removal of the body burden of excessive amounts of CO remains to be fully evaluated in clinical trials.

The following table (Table 9-1), based on the Haldane relationship for resting individuals, indicates the equilibrium percentage saturation of the Hb with CO at various alveolar pressures of CO (alveolar P_{O2} is assumed to be 98 torr).

DISTRIBUTION IN BODY TISSUES

In a discussion of the intracellular effects of CO, consideration must be given to the interactions of all substances within the tissue cells involved with O_2 delivery. Since Hb and myoglobin are structurally related, they react with CO in a similar manner. The function of myoglobin (*in vivo*) may be to act as a reservoir for O_2 within the muscle fiber. There are approximately 132 g of myoglobin in the muscles of a 70-kg man. The turnover rate is on the

TABLE 9-1. PERCENT COHb VERSUS CO PRESSURE

		CO	
%COHb	ppm	% Atmosphere	Torr
0.87	5	0.0005	0.0038
1.73	10	0.001	0.0076
3.45	20	0.002	0.0152
5.05	30	0.003	0.0248
6.63	40	0.004	0.0304
8.16	50	0.005	0.0380
9.63	60	0.006	0.0456
11.08	70	0.007	0.0532
12.46	80	0.008	0.0608
13.80	90	0.009	0.0684
15.11	100	0.010	0.0760
16.37	110	0.011	0.0836
17.60	120	0.012	0.0912
18.78	130	0.013	0.0988
19.95	140	0.014	0.1064
21.05	150	0.015	0.1140
22.15	160	0.016	0.1216
23.23	170	0.017	0.1291
24.26	180	0.018	0.1368
25.25	190	0.019	0.1442
26.22	200	0.020	0.1520

order of 0.34 mg/day. The CO and O_2 equilibria of human myoglobin (in vitro) has been studied and a hyperbolic O_2 dissociation curve established.[55] This curve, unlike the hemoglobin one, is not affected by the hydrogen ion concentration, the ionic strength, or the concentration of myoglobin. The relative affinity constant, M, is approximately 40 but is still sufficient to induce appreciable formation of carboxymyoglobin (COMb). Coburn et al.[11,13] as well as Luomanmaki[37] have studied the interrelationships between COHb and COMb. Coburn's work with ^{14}CO has shown that identical CO exposures can produce different degrees of saturation of Mb, depending upon the partial pressures of O_2 in blood and tissue. Coburn and associates[13] determined that the ratio of CO content in muscle to the content in blood is a function of arterial P_{O2}. This ratio, for skeletal muscle, was found to be approximately one, but in myocardial tissue it was three. When arterial P_{O2} fell below 40 to 30 torr, CO disappeared from the blood, presumably entering the muscle. A substantial amount of extravascular CO stores are located in muscle. The higher ratio for cardiac tissue may be of considerable significance. In an individual with a blood COHb level of 10 percent, some 30 percent of cardiac myoglobin may be saturated with CO. Coburn and his associates[13] were able to estimate the mean P_{O2} of skeletal muscle and myocardium, finding these to be six to eight and four to six torr, respectively.

Although no final judgment can be made regarding the next lower step involved in O_2 transport--i.e., the role of cytochromes a_3 and P-450--the fact that experimentally they react with CO as do other heme-containing substances suggests that they may play a role in CO poisoning. The evidence suggests that interactions between CO and cytochrome oxidases are of minor significance at the concentrations of CO found in community air pollution. All of the data on the cytochromes have been obtained from in vitro experiments. Whether similar events occur in vivo remains uncertain. The most likely oxidase for inhibition in vivo is P-450, but no convincing evidence for this effect is available. Cooper et al.[17] have reported that the ratio of CO to O_2 required for 50 percent inhibition is approximately one to one, in contrast to the similar ratio for cytochrome a_3 of between 2.2 and 2.8. Root[54] believes that at a P_{CO} compatible with life, only insignificant blocking of the O_2 consumption system occurs. In terms of total distribution throughout the body of an inhaled dose of CO, the amounts bound to these hemoproteins are small compared with the amounts bound to Hb and Mb. Coburn[11] has diagrammed a representation of the factors influencing body CO stores. The possible significance of these hemoproteins lies in the concept that under conditions where tissue P_{O2} is decreased, the affinity of intracellular hemoproteins for CO may increase.

SUMMARY

One of the primary functions of Hb is to provide for the transport of O_2 and CO_2. Hemoglobin combines readily with either O_2 (to form O_2Hb) or CO (to form COHb). The affinity of Hb for CO is some 240 times greater than its affinity for O_2. The presence of COHb in blood not only reduces the availability of O_2 to the body, but its presence inhibits the dissociation of the remaining O_2. Carbon monoxide also combines reversibly with heme compounds in the cell.

Carbon monoxide is available primarily from two sources--exogenously from the ambient air and endogenously from the catabolism of pyrrole rings originating from heme-containing pigments. Endogenous sources of CO result in COHb levels of approximately 0.5 percent in normal males. Any increment above this level arises from exogenous sources. The primary factors determining the final level of COHb are the concentration of inspired CO, alveolar ventilation, red cell volume, barometric pressure, and the diffusive capability of the lungs. The uptake and final equilibrium level have been fairly well characterized, but the excretion of CO requires further clarification. The excretion appears to be biphasic--a rapid exponential fall followed by a slower rate of decline.

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10. EFFECTS OF CARBON MONOXIDE ON EXPERIMENTAL ANIMALS

INTRODUCTION

The interpretation of comparative data from species other than man must be carried out because there are species differences in the particular findings. However, an attempt must be made to generalize the principles, rather than the particulars, from other species to man. For instance, it would not be surprising if the threshold level for CO effects on the cardiac system in the rat would differ from the threshold level in man, but it would be less likely that the effect would be salubrious in the rat but deleterious in man. The non-human experiments, although they must be interpreted rather than simply transferred to man, serve the valuable ends of (1) suggesting studies to be verified in man, (2) exploring the properties and principles of an effect much more thoroughly and extensively than is possible in man, (3) protecting human subjects from unwarranted exposure, (4) permitting a compression of exposure duration in relation to aging as a result of the shorter life expectancies of animals, and (5) providing tissues, organs, and cellular material more readily, allowing more precise observation of specific functions.

Fortunately, our knowledge of the influence of CO on biological systems is not limited to studies on non-human animals. Many direct experiments on humans have been carried out during the last century. While many reports describe inadvertent exposures to various levels of CO, there are a considerable number of precise and delineated studies utilizing human subjects. Most of these have been conducted by exposing young adult males to concentrations of CO equivalent to those frequently or occasionally detected during routine surveys at various ambient monitoring stations.

SELECTION OF ANIMAL MODELS

Animal studies have provided valuable insights into both the potentially adverse effects of CO and the basic mechanisms by which this gas influences physiological processes. However, many studies have utilized extraordinary levels of CO, i.e., levels rarely found in ambient air. These studies are not being considered in this chapter except as parts of dose-response curves or as clues to processes, since the toxic effects of very high levels of CO have been well documented for both animals and man. Unfortunately, the oxygen (O_2) dissociation curves of the animals utilized in CO studies are not equivalent. There are also questions as to the relative CO affinities of hemoglobin (Hb) in various animal species. Klimisch et al.[53] reported that the blood of hamsters has the greatest affinity for CO, followed by rats, pigs, and rabbits, respectively.

All of the effects reported later have been shown to occur to some degree in most animals studied (mice, rats, rabbits, dogs, and monkeys). Some differences between species have been reported, but no definitive studies designed to elucidate special sensitivities have been made. Long-term exposures of animals to sufficiently high concentrations of CO, producing levels of COHb from 20 to 40 percent, can induce pathological changes in the heart and brain. As in acute high level intoxication in man, serious sequelae also develop in animals.

Species differences in response are ideally illustrated in the studies by DeBias et al.[24-26] on dogs and cynomolgus monkeys (Macaca irus irus). Chronic exposure (23 hours per day over several months) to 115 mg/m^3 (100 ppm) CO resulted in COHb levels of 14 and 12.4 percent in dogs and monkeys, respectively. The dogs remained in clinically good health with no untoward signs that could be interpreted as being CO-induced.[25] Serum enzymes, hematological parameters, and electrocardiograms did not change significantly. Carbon monoxide exposure of normal monkeys resulted in myocardial effects. Experimentally infarcted monkeys had greater P-wave amplitudes and increased evidence of T-wave inversions than normal monkeys similarly exposed. Jones et al.[49] exposed rats, guinea pigs, dogs, and monkeys to 58, 115, or 230 mg/m^3 (50, 100, or 200 ppm) CO continuously for 90 days. Hematocrit and Hb levels were unchanged at the lowest level of CO exposure but were significantly elevated at the two higher levels in all animals except the dogs. Theodore et al.[99] have summarized the extensive data collected at the Aerospace Medical Research Laboratory. Rhesus monkeys, baboons, dogs (beagles), rats, and mice were exposed for 71 days to CO concentrations of 460 mg/m^3 (400 ppm). Pathological studies of these animals showed that large animals had no changes in the central nervous system (CNS) or in the heart. Cardiac changes in the rat were the only positive findings.

The above studies have been cited as examples of the particular differences among species; they illustrate the need for caution in generalizing these findings to man. In any interpretation of these findings, the principles, rather than the particulars, should be generalized.

NERVOUS SYSTEM AND BEHAVIOR

General Activity and Sleep

Several authors report effects of CO on gross or overall behavior such as general activity, sleep, and motor performance. Colmant[20] found disturbances in the sleep patterns of rats exposed to as little as 288 mg/m^3 (250 ppm) for 96 hours or 345 mg/m^3 (300 ppm) for 5 hours. Lower levels of exposure did not affect sleep and higher levels produced progressively greater disturbances. Female rats exposed by Fechter and Annau to 174 mg/m^3 (150 ppm, 15 percent COHb) during the full term of their pregnancies produced offspring which at first showed reduced activity levels and lowered body weights.[35] At 21 days postpartum, however, no differences existed between offspring of CO-exposed mothers and controls. Apparently, at much higher levels of exposure neonatal and adult rats develop hyperactivity rather than reduced activity levels.[21] These levels of exposure produce brain damage from which neonates, but not adults, recover. Plevova and Frantik[85] have reported decreased motor endurance in rats exposed by two different uptake rates produced by using different CO concentrations for sufficient time to reach the target and produce COHb concentration of 20 percent. High uptake rates, while producing equivalent COHb levels, had significantly greater effects than low uptake rates. Lewey and Drabkin[56] demonstrated alterations in gait in dogs exposed for 11 weeks to 115 mg/m^3 (100 ppm) CO (20 percent COHb). Musselman et al.[70] showed no effect on rats activity levels as a result of 58 mg/m^3 (50 ppm) exposure for 3 months.

Learning and Performance

Using a wide variety of behavioral paradigms, a number of investigators have shown effects of CO upon the acquisition of new behavior and/or the performance of already learned tasks. Zorn[118] exposed rats to 174 mg/m^3 (150 ppm, 10 percent COHb) for 8 hours each night for 2, 4, and 10 weeks and showed that such exposures reduce efficiency of shock-escape behavior at all exposure durations. Goldberg and Chappell,[41] using a continuous food reinforcement schedule in a lever-press task with rats, showed reductions in response rate at exposure levels of 230 to 288 mg/m^3 (200 to 250 ppm) CO for 2 hours. They also showed adverse effects of such exposures on the performance of a variable ratio task. Xintaras et al.[113,114] showed no effects on the performance of a fixed interval lever press for food reinforcement in rats exposed to 115 mg/m^3 (100 ppm) CO for 2 hours.

Using more complicated schedules of reinforcement and/or more complicated tasks, perhaps involving more "cognitive" behavior, other investigators have shown much higher thresholds for CO effects. Merigan and McIntire,[65] Ator et al.,[8] and Smith et al.[92] used a small number of rats in progressive ratio, differential-reinforcement-of-low-rates, and fixed-consecutive-number schedules, respectively. They showed no statistically significant effects below about 690 mg/m^3 (600 ppm) CO, but with the small number of subjects it is possible that effects were hidden by high variability. Theodore et al.[99] report no statistically significant effects in 12 rhesus monkeys on very complicated long-term, multi-schedule, aversively controlled performance tests with CO exposures as high as 575 mg/m^3 (500 ppm) for 100 days, even though the subjects "appeared to be ill." It should be borne in mind that aversively controlled task performance is remarkably stable and insensitive to environmental conditions. These investigators also progressively increased CO level rather than exposing subjects to the high level initially and so could have induced behavioral adaptation, but no control group was included to test this possibility. Johnson et al.[48] used only three rhesus monkeys and found no effects from CO levels of up to 575 mg/m^3 (500 ppm, 44 percent COHb) for 14 days on a food-reinforced time discriminations task. McMillan and Miller[64] found definite effects at CO levels as high as 1150 mg/m^3 (1000 ppm) for 1.5 hours using a multiple fixed-ratio/fixed-interval schedule with pigeons. They showed, however, that at about 575 mg/m^3 (500 ppm) CO for 1.5 hours, the response of pigeons to d-amphetamine was altered with respect to controls. Pigeons, on such schedules of reinforcement, tend to be very stable responders in the face of environmental alterations.

Carter et al.[16] report that rats exposed to 1150 mg/m^3 (1000 ppm) CO for 1.5 hours had drastically reduced response rates on a food-reinforced fixed-ratio schedule task. If, however, carbon dioxide (CO_2) was added at 2.5, 5.0, and 7.5 percent levels to the CO-containing air, performance was progressively and substantially improved. This was apparently due to increased cerebral blood flow initiated by the CO_2; CO_2 levels by themselves produced no behavioral effect.

Electrophysiological Effects

It is not unlikely that central nervous system (CNS) electrophysiological measures could provide sensitive indices of pollutant effects. Dyer et al.[31] exposed pregnant rats to 174 mg/m^3 (150 ppm, 15 percent COHb) for their full term. Offspring were tested at 79 days of age, and it was shown that some components of the cortical visually evoked responses increased in amplitude in the females but not in the males. Using direct exposures to CO levels from 174 to 1150 mg/m^3 (150 to 1000 ppm) in adult rats, Dyer and Annau[30] showed marginally increased amplitude in some superior colliculus visually evoked potentials at 575 mg/m^3 (500 ppm) CO or greater. Clearly increased latencies in all evoked potential components were shown only at a level of 1150 mg/m^3 (1000 ppm). Xintaras et al.[113,114] reported similar results in superior colliculus preparations in rats exposed to 115 mg/m^3 (100 ppm) for 2 hours, but because of the lack of statistical analysis, it is difficult to evaluate these findings. Xintaras et al. pointed out that increased evoked potentials are similar to those found under administration of sodium pentobarbitol and those found when the animal is going to sleep. Petajan et al.[83] report that at high CO levels (2875 mg/m^3, 2500 ppm, 60 to 70 percent COHb), cortical visually evoked responses are attenuated.

Annau[4] reports that rats that have been trained to press a lever for the reward of an electrical stimulation to the hypothalamus show slightly reduced response rates when exposed to as little as 174 mg/m^3 (150 ppm) CO for 16 minutes while they were responding. Higher concentrations produced greater decrements. These decrements represented early effects of CO, before COHb equilibrium was reached. It was also shown, in another part of the same study, that with an exposure to 1150 mg/m^3 (1000 ppm) CO the decline in response rates correlated highly with an increase in COHb. They also reported data that indicated that CO had more temporary and less severe effects than hypoxic hypoxia, which reduced venous Po_2 to equivalent levels.

Pankow et al.,[80] using rats given subcutaneous injections of CO sufficient to produce 19 percent and 60 percent COHb in two exposure levels, showed that both levels decreased sciatic nerve conduction velocity for a period of up to 28 days following exposure. Grunnet and Petajan,[42] using 2875 mg/m^3 (2500 ppm) CO exposures until peroneal or ventral caudal nerve conduction was lost, showed a deterioration of Schwann cells, which regenerated by 14 to 21 days. Shul'ga[91] showed effects on motor chronaxie, CNS pathology, and porphyrin levels by CO levels as low as 29 mg/m^3 (25 ppm) for 8 hours per day for 10 weeks. Pathological changes and porphyrin levels were not quantitatively documented.

Cerebral Blood Supply

Zorn[118] measured various parameters of cerebral blood supply in unanesthetized cats, rats, and rabbits with exposure levels ranging from 115 to 805 mg/m^3 (100 to 700 ppm) CO. In all cases cerebral, subcortical, and liver Po_2 measures declined as a linear function of COHb, with Po_2 recovery lagging behind COHb elimination. Miller and Wood,[66] on the other hand, using anesthetized and artificially respirated rats exposed to 575 and 1150 mg/m^3 (500 and

1000 ppm), showed about twice the rate of Po_2 decline in the liver as in the brain. Their findings in the brain were similar to those of Zorn.[118] Traystman[104] showed that cerebral blood flow in anesthetized dogs increased as a nearly linear function of COHb. Similar results were shown for unanesthetized goats by Doblar et al.,[28] who also found that O_2 delivery to the brain decreased as a function of COHb and showed no clear threshold. It would appear from Traystman's and Doblar's data that Po_2 might not fall as rapidly in cerebral tissue as in other tissues because of increased cerebral blood supplies. This hypothesis seems to be supported by Miller and Wood's[66] data but not by Zorn's.[118] Traystman,[104] on the other hand, did not measure blood flows in other body systems in order to test the notion that there was not simply an overall vasodilatory response. The amount of hypoxia was indirectly assessed by Sokal[93] using rats and measuring glucose, pyruvate, lactate, and blood pH levels in the brain after exposure to either 11,500 mg/m^3 (10,000 ppm) for 4 minutes or 4,600 mg/m^3 (4,000 ppm) for 40 minutes. The slower uptake rates produced more extreme effects.

CNS Pathology and Biochemical Alterations

Carbon monoxide poisoning studies where CO levels are very high have commonly produced central nervous system lesions as a result of local and widespread anoxia. Experimental results using high level CO exposure have been used to infer such brain damage as an explanatory mechanism[73] and have demonstrated ultrastructural evidence for such damage.[72] Preziosi et al.[86] exposed dogs on varying short-term exposures sufficient to produce COHb levels of 40 to 50 percent and on various long-term exposure schemes (6 weeks), which produced COHb levels as low as 4 to 12 percent. Short-term, high level exposures produced varying (only qualitatively described) CNS pathologies ranging from mild microglial reactions to localized necrotic lesions. Long-term, low level exposures produced brain ventricular dilation but no other pathological signs. From the article it is difficult to judge the extent or frequency of the control-experimental differences.

Lewey and Drabkin,[56] using dogs exposed for 11 weeks at 115 mg/m^3 (100 ppm CO, 20 percent COHb), demonstrated localized CNS lesions owing to anoxia, similar to but much less in extent than those in acute CO poisoning. Ginsberg and Myers,[40] using pregnant rhesus monkeys with short-term CO exposure just before delivery, showed that COHb levels in offspring ranged between 10 to 20 percent for a few hours, which was much lower than maternal COHb (60 percent). Neurological (CNS) damage in the offspring ranged from none to severe and was inversely correlated with arterial Po_2 values present during exposure. All mothers showed no clinical effects after recovery, despite much higher levels of exposure. Theodore et al.[99] showed no brain pathology in dogs and monkeys after 168 days of exposure to 460 to 575 mg/m^3 (400 to 500 ppm) CO. Histopathological examination of the brains of monkeys exposed to as much as 77.6 mg/m^3 (67.5 ppm) CO for 22 hours a day for 2 years were normal. Dykyk et al.[29] reported no ultrastructural damage in either mother rats or fetuses when mothers were exposed to 1 percent CO for 60 minutes just before delivery (mother's COHb = 73.3 percent, fetuses' COHb = 10.3 percent). These investigators did, however, show increased O_2 uptake in CNS giant reticular formation cells in fetuses but a decreased O_2 uptake in the same cells in mothers.

Fechter and Annau[35] exposed female rats to 174 mg/m^3 (150 ppm CO, 15 percent COHb) during their entire terms of pregnancy and found reduced levels of dopamine and CNS protein in offspring. Miller and Wood,[66] using rats exposed to 575 mg/m^3 (500 ppm) and 1150 mg/m^3 (1000 ppm) CO until COHb equilibrium was reached, showed changes in brain energy metabolism; however, the changes were smaller than predicted from theory. At high levels of CO exposure (1150 mg/m^3, 1000 ppm, for 4 hours) Newby et al.[71] demonstrated decreased dopamine synthesis but no alterations in norepinephrine levels in rats. Szumanska et al.[98] using 1 percent CO for 20, 60, and 90 minutes did show decreases in norepinephrine and catecholamine levels. Marks and Swiecicki,[61] however, exposed rats to one percent CO for 120 minutes and showed increased CNS catecholamine levels.

Summary and Conclusion of Studies on CO's Effects on Nervous System and Behavior in Experimental Animals

Table 10-1 shows a summary of all of the reviewed studies pertinent to experimental animals, CNS, and behavior. From the data we may conclude that definite effects of CO may be seen in general overt behavior at 230 mg/m^3 (200 ppm) and possibly as low as 115 mg/m^3 (100 ppm), depending on the species and test employed. In learning and performance the effect on the particular task being performed appears to be critical, with simple task performance being affected above 174 mg/m^3 (150 ppm), but more complex or demanding task performance not being affected until 575 to 690 mg/m^3 (500 to 600 ppm). The effects of CO on learning might have varied among studies shown in Table 10-1 as a result of factors other than complexity of the task or schedule requirements, but these seem to be the major variables. Electrophysiological measures in the CNS seem to provide highly variable data with only two studies by the same group showing consistent effects below 500 ppm. Methodological differences were very great in electrophysiological studies, and results were not as clearly related to function as were behavioral data. Only one study measured peripheral nerve activity at very low levels of CO, and that study[91] should be replicated. Cerebral blood supply measures seem to indicate a close relationship between tissue Po_2 and COHb levels, despite the fact that cerebral blood supply is increased by COHb increases. At higher levels of COHb, brain damage and alterations in brain chemistry are reported.

The results reviewed in this document would be more easily interpretable if the general quality of experimental procedures, design, and analysis were improved. In none of the studies, for instance, was the use of blind analysis reported. This is important because (1) the handling of animals can influence the results of some experiments, and (2) the data are sometimes treated only qualitatively. In some of the studies, appropriate control groups were not run. Sometimes COHb levels were not reported.

An almost universal problem was the use of inappropriate statistical tests, such as multiple t-tests where analysis of variance was appropriate, or univariate analysis where multivariate analysis should have been used. This misuse of tests usually leads to underestimated p-values and, as a result, to overestimates of the number of effects declared

TABLE 10-1. SUMMARY OF EFFECTS OF CO ON CENTRAL NERVOUS SYSTEM AND BEHAVIOR OF ANIMALS

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Colmant[20]	Rat n = 28	250-300 ppm, 5-96 hr		Sleep cycles.	Less REM at all exposure levels.	
Fechter and Annau[34,35]	Rat n = 16-32 (pups)	150 ppm during full term of pregnancy	15% (maternal)	Open field activity in offspring.	Reduced through 14 days but normal by 21 days of age.	
Culver and Norton[21]	Rat n = 24-40 (pups) n = 16-32 (adults)	1000 ppm until respiratory failure		General activity in residential maze.	Neonates increased but recovered by 3 mo. Adults increased slightly, no recovery.	Extremely high exposure, probably produced brain damage.
Plevova and Frantik[85]	Rat n = 18	200 and 700 ppm, 30 min and 24 hr	20%	Motor (running) endurance.	Reduced endurance.	Two exposure levels were used to produce same COHb at two saturation rates.
Lewey and Drabkin[58]	Dog n = 6	100 ppm, 11 wk	20%	Locomotion.	Mildly disturbed gait but no other "clinical" symptoms.	No control group, only qualitative results.
Musselman et al.[70]	Rat n = 100	50 ppm, 3 mo		Activity level.	No effects.	
Zorn[118]	Rat n = 240	150 ppm, 8 hr/day for 2, 4, and 10 wk	10%	Shock escape-avoidance.	Reduced performance.	
Stupfel & Bouley[95]	Rat n = 336 mouse n = 76	50 ppm, 95 hr/wk, whole natural life expectancy (also short-term)		Shock escape-avoidance.	No effects.	

TABLE 10-1. (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Goldberg and Chappell[41]	Rat n = 16 in each of 2 tasks	200, 250 and 500 ppm, 2 hr		Continuous and variable ratio schedules, lever press for food.	Reduced rates in both tasks and all levels.	
Xintaras et al.[113,114]	Rat n = 10	100 ppm, 2 hr		Fixed interval schedule lever press for food.	No effects.	Also collected electrophysiological measures.
Smith et al.[92]	Rat n = 4	200, 400, and 600 ppm, for 60 min during performance		Fixed-constant number schedule, lever press for food.	No consistent effect until 600 ppm.	Complicated schedule might not be affected. Small number of subjects.
Ator et al.[8]	Rat n = 4	100, 250, 500, and 750 ppm, 2 hr	22-57%	Differential reinforcement of low rate, lever press for food.	No effect until 750 ppm.	Schedule produces extremely stable data. Might not be affected by COHb. Small number of subjects.
Merigan and McIntire[65]	Rat n = 4	155, 330, 520, and 700 ppm, 30 min preperformance plus up to 1 hr during performance		Progressive ratio schedule, lever press for food.	No effect until 500-700 ppm.	Complicated schedule might not be affected. Small number of subjects.
Theodore et al.[99]	Rhesus monkey n = 12	400-500 ppm, 168 days	32-38%	Complicated series of shock avoidance, lever press.	No effects.	Aversive control of behavior produces stable results, less sensitive to environmental effects.
Johnson et al.[48]	Rhesus monkey n = 3	150, 200, 250, and 500 ppm, 1-8 days	13-44%	Time discrimination lever press for food.	No effects.	Small number of subjects.

TABLE 10-1. (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
McMillan and Miller[64]	Pigeon n = 8	380, 490, 930, and 1410 ppm, 1 hr + test session		Multiple schedule (fixed interval, fixed ratio), key peck for food.	No effects lower than 500 ppm.	Showed interaction of CO with d-amphetamine.
Carter et al.[16]	Rat n = 10	1000 ppm, 1.5 hr (also added CO_2)		Fixed ratio schedule, lever press for food.	Severe depression of rate.	Added CO_2 restores response rates to some extent.
Dyer et al.[31]	Rat n = 41 (pups)	150 ppm for full term of pregnancy	15% (maternal)	Cortical visual-evoked potential.	Increased amplitude but only in females.	
Dyer and Annau[30]	Rat n = 8	150, 250, 500, and 1000 ppm, 2 hr	15-58%	Superior colliculus visual-evoked potential.	Increased amplitude at 500 ppm; decreased amplitude at 1000 ppm.	
Xintaras et al.[113,114]	Rat n = 10	100 ppm, 2 hr		Superior colliculus visual-evoked potential.	Increased amplitude; decreased peak latencies.	Measurements made while lever pressing on fixed interval schedule for food.
Petajan et al.[83]	Rat n = 45	2500 ppm until ventral cortical nerve conduction stopped	60-70%	Cortical visual-evoked potential and nerve conduction velocity.	Decreased measures at 60-70% COHb.	Very high levels at high saturation rates.
Annau[4]	Rat n = 12	150, 250, 500, and 1000 ppm		Lever press for hypothalamic electrical stimulation (reward).	Decreased rates as a function of CO beginning with slight effects at 150 ppm.	
Pankow et al.[80]	Rat n = 47	Subcutaneous injection of CO to produce two COHb levels	19% and 60%	Sciatic nerve conduction velocity.	Decreased velocity at both levels up to 28 days but back to normal at 90 days.	

TABLE 10-1. (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Grunnet and Petajan[42]	Rat n = 20	2500 ppm until ventral nerve conduction stopped	60-70%	Peripheral nerve pathology.	Degenerated Schwann cell, regenerated 14-21 days.	Very high levels at high saturation rates.
Shul'ga[91]	Rat n = 24	25 and 2 ppm for 8 hr/day, 10 wk		Motor chronaxie, CNS pathology, and porphyrin levels.	25 ppm increased chronaxie, depressed porphyrin, and produced CNS gross pathology.	CNS damage and for porphyrin levels not quantitatively documented.
Zorn[119]	Cat and rat 5-20 per group	100-700 ppm in unanesthetized animals		Po_2 and COHb in brain and liver.	Po_2 decreased as a linear function of COHb at same rates for brain and liver.	
Miller and Wood[66]	Rat	500 and 1000 ppm in anesthetized animals for 25 hr		Po_2 and COHb in brain and liver.	Po_2 decreased more for liver than brain.	
Traystman[104]	Dog n = 23	CO of various amount to produce target levels of venous Po_2	2.5-50%	Cerebral blood flow.	Flow increased as COHb increased.	
Doblar et al.[28]	Goat n = 6	CO of various amount to produce target levels of venous Po_2	0-70%	Cerebral blood flow.	Flow increased as COHb increased.	
Sokal[93]	Rat n = 27-34	10,000 ppm, 4 min and 4000 ppm, 40 min	50%	Glucose, pyruvate, lactate, and blood pH levels in brain.	Increases in all levels except decrease in blood pH.	Slow saturation rate produced more extreme effects.

TABLE 10-1. (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Norton and Culver,[72] Norton et al.[73]	Rat n = 24	1000 ppm until respiration stopped		CNS pathology.	Ultrastructural evidence for brain damage.	
Preziosi et al.[86]	Dog n = 46	50-100 ppm, various times per day (4-24) up to 6 wk	7-12%	CNS pathology.	Brain lesions of various types similar to CO poisoning but more localized.	COHb levels lower than would be expected from exposure level.
Ginsberg and Myers[40]	Rhesus monkey n = 9 (pregnant females)	3000 ppm to produce 60% COHb just before delivery	60%	CNS pathology in offspring.	Ranged from severe brain damage to no effects.	COHb in fetuses did not nearly approach that of mothers.
Theodore et al.[99]	Monkey n = 9 Dog n = 16 Rat n = 136 Mouse n = 80	400-500 ppm 168 days	32-38% (dogs and monkeys only)	CNS pathology.	No effects.	
Dykyk et al.[29]	Rat (mothers n = 28, fetuses n = 32, neonates n = 24)	Mothers exposed to 1% CO for 60 min at term	Mothers 73.3% Fetuses 10.3%	O_2 consumption by reticular formation giant cells. Histology exams.	Increased 4-fold in fetus; decreased in mothers. No histological differences.	
Eckardt et al.[30]	Cynomolgus monkey n = 27	20 and 67.5 ppm, 22 hr/day for 2 yr	2.0-5.5% and 4.8-10.0%	CNS histopathology.	No effects.	COHb varied unusually widely.
Fechter and Annau[32,33]	Rat n = 16-32 (pups)	150 ppm during full term of pregnancy	15% (maternal)	Brain chemistry.	Reduced dopamine and brain protein.	

TABLE 10-1. (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Miller and Wood[66]	Rat	500 and 1000 ppm for 2.5 hr	33-52%	Brain chemistry.	Reduced energy metabolism.	Smaller than predicted from theory.
Szumanska et al.[96]	Rat	1% CO for 20, 60, and 90 min		Brain chemistry.	Reduced noradrenalin and catecholamine levels. Recovered later.	
Newby et al.[71]	Rat	1000 ppm, 4 hr		Brain chemistry.	Dopamine synthesis rate decreased, noradrenalin did not.	

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25^{0}C, 760 torr.

significant.[87] From the statistical considerations alone, one would be led to suspect that the effects of CO are less extreme than reported in the literature but most results were still significant when conservative corrections were applied by the reviewer.

For many studies, it is difficult to answer such basic questions as the number of subjects run, the statistical method used, the exact experimental designs employed, etc. An effort has been made in this literature review to interpret the results from a consistent framework.

Apparently the simpler behavioral tasks and general activity measures yield the lowest thresholds for CO effects. These appear at about 115 to 230 mg/m^3 (100 to 200 ppm) for exposure periods long enough to approach saturation.

CARDIOVASCULAR SYSTEMS

The various tissues of the body must receive O_2 at a rate adequate to maintain their normal functions. Carbon monoxide, when present even at very low partial pressures, can seriously impair the O_2 transport system. Experimental studies of animals have provided insights into the mechanisms by which CO modifies cardiovascular functions. The presence of COHb interferes with tissue oxygenation by increasing the concentration of carboxymyoglobin (COMb). The ratio of COMb to COHb can increase from 1.0 to 2.5 in skeletal muscles and myocardium if the arterial O_2 tension is 40 torr or lower.[19]

Cardiac Performance and Damage

Fusco et al.[36] found abnormal electrocardiograms (EKG) and changes in ventricular and arterial pressures in dogs exposed to CO. Lewey and Drabkin[56] and Ehrich et al.[33] exposed dogs to 115 mg/m^3 (100 ppm CO, 20 percent COHb) for 11 weeks, 5.75 hours per day, and showed EKG abnormalities and cardiac hypertrophy, muscle degeneration and necrosis. Lindenberg et al.[57] exposed dogs to 58 and 115 mg/m^3 (50 and 100 ppm CO, 2.6 and 5.5 percent COHb) CO continuously and intermittently, seven days a week for six weeks, and observed abnormal EKGs in all dogs and histological evidence of cardiac muscle degeneration in some subjects. Effects were more pronounced at the higher exposures. Preziosi et al.[86] exposed dogs continuously to 115 mg/m^3 (100 ppm) for six weeks and reported abnormal EKGs, right and left heart dilation, and myocardial thinning. Histological examination showed old scarring in some cases and fatty degeneration of heart muscle in others. Carboxyhemoglobin levels of 7 to 12 percent were lower than would be predicted from the exposure. Musselman et al.[70] exposed dogs to 58 mg/m^3 (50 ppm) CO for 24 hours a day, seven days a week for three months. No changes in the electrocardiogram or heart rates were observed. Examination of organs and tissues revealed no pathological changes after exposure.

Monkeys (Macaca irus) were exposed to 288 mg/m^3 (250 ppm, 20.6 percent COHb) CO for two weeks by Thomsen.[100] In all animals so exposed, the coronary arteries showed more or less pronounced widening of the subendothelial spaces in which cells with or without lipid droplets were accumulating. He suggested that monkeys were more sensitive to CO than the rabbits.

Eckardt et al.[32] exposed cynomolgus monkeys (22 hours a day, 7 days a week for 2 years) to 23 or 77.5 mg/m^3 (20 or 67.5 ppm) CO. Carboxyhemoglobin levels showed considerable variation during the experimental period, from 2.0 to 5.5 percent and 4.8 to 10.2 percent for low and high CO ambient environments, respectively. No cardiac effects were noted at these levels. Penney et al.[81,82] studied the influence of CO on the development of cardiac hypertrophy in the rat. Exposure to various CO levels of 115 to 575 mg/m^3 (100 to 500 ppm) for 20 to 46 days, leading to COHb levels of 9.2 to 41 percent, resulted in hypertrophy of both right and left ventricles. Stupfel and Bouley[95] exposed mice and rats for 95 hours per week to 58 mg/m^3 (50 ppm) CO either for 1 to 3 months or for their natural life expectancy of up to 2 years. They made a large number of measurements during exposure, in addition to pathological examination after death. They observed no important effects of the CO exposure on their animals.

Thomsen and Kjeldsen[102] exposed rabbits to 58, 115, and 207 mg/m^3 (50, 100 and 180 ppm; 4.5, 9.0, and 17.0 percent COHb) CO and demonstrated aortic focal intimal lesions beginning at exposure levels of 207 mg/m^3 (180 ppm) for 4 hours. Kjeldsen et al.,[52] exposing rabbits to 207 mg/m^3 (180 ppm) CO for 2 weeks (16.7 percent COHb), reported degenerative changes such as contraction bands, myofibrillar disintegration, myelin body formation, and dehiscence of the intercalated disks. Thomsen and Kjeldsen[101] determined the threshold for such effects to be about 115 mg/m^3 (100 ppm) for 4 hours (8.5 percent COHb).

Cardiac hypertrophy was demonstrated by Tumasonis and Baker[106] in chick embryos that had been exposed to 490 mg/m^3 (425 ppm, 25.4 percent COHb) for 144 and 168 hours. Based on experiments with a wide variety of animals exposed to 460 to 575 mg/m^3 (400 to 500 ppm) CO (approximately 32 to 38 percent COHb in dogs and monkeys) for 168 days, Theodore et al.[99] were unable to demonstrate any cardiac abnormalities.

Cardiac Fibrillation Threshold

Continuous exposure of cynomolgus monkeys to 115 mg/m^3 (100 ppm; 12.4 percent COHb) CO for 3 to 6 months resulted in demonstrable electrocardiographic effects in both normal monkeys and monkeys with myocardial infarction.[23,25] These investigations also considered the susceptibility of the ventricles to induced fibrillation.[24] Normal and infarcted monkeys were exposed to 115 mg/m^3 (100 ppm) CO for 6 hours. The voltage required to induce fibrillation was highest in monkeys exposed to normal air and lowest for infarcted animals breathing CO. Animals with either infarction alone or CO alone each required significantly less voltage for fibrillation; when the two were combined, the effects were additive. In contrast to these findings, it has been shown that as a result of intermittent exposure to CO [575 mg/m^3 (500 ppm), 6-minute pulses of CO each hour for 12 hours each day over a period of 14 months], cynomolgus monkeys fed either a normal or a semipurified cholesterol diet, did not show myocardial infarctions or electrocardiographic abnormalities.[60] In these animals, blood COHb reached 21.6 percent at the end of the daily period. Aronow et al.[5] observed in a blind randomized study that 21 dogs with acute myocardial injury had a reduction in ventricular fibrillation threshold after breathing 115 mg/m^3 (100 ppm) CO for 2 hours (6.3 percent COHb).

Cholesterol and Sclerosis

Astrup et al.[6,7] reported data showing increased aortic cholesterol accumulation and atheromatosis in rabbits exposed to 196 mg/m^3 (170 ppm) CO for 8 weeks and then to 350 ppm for 2 more weeks (17 to 33 percent COHb). Webster et al.[108] experimented with squirrel monkeys and found no effects on aortic or carotid vessels or on serum cholesterol. They did note a greater incidence of coronary atherosclerosis in groups exposed to 115 to 345 mg/m^3 (100 to 300 ppm, 9 to 26 percent COHb) CO on an intermittent schedule for 7 months. Results essentially identical to those found by Webster et al.[108] were reported by Davies et al.[22] using rabbits exposed intermittently for 10 weeks to CO concentrations to produce 20 percent COHb. Malinow et al.[60] reported no aortic or coronary atherosclerosis in cynomolgus monkeys exposed on an intermittent schedule for 14 months so as to produce daily accumulations of 21.6 percent COHb.

Stender et al.,[94] in Astrup's group, attempted to resolve the apparent conflict in the above studies, regarding aortic atherosclerosis, by exposing rabbits to 230 mg/m^3 (200 ppm) CO continuously for 12 hours per day for 6 weeks. Instead of using a constant high cholesterol diet for all subjects, the serum cholesterol was held constant by variations in diet cholesterol. In this case, no aortic cholesterol or atherosclerotic differences were seen between CO-exposed and control groups. In reference to earlier results, Astrup et al.[6] now interpret these data to mean that observed damage in earlier studies was attributable to greatly increased serum cholesterol in CO groups, although Davies et al.,[22] Webster et al.,[108] and Malinow et al.[60] reported no increased serum cholesterol either. Differences in cholesterol buildup in aortic tissue (as a result of CO exposure) might be related to observed differences caused by CO exposure in lactate dehydrogenase (LDH) enzymes in rabbits, as observed in the aorta by Hellung-Larsen et al.[43] Penney et al.[81,82] also reported increased LDH in rats. However, in the most recent studies by Astrup's group (Hugod et al.[46]), non-cholesterol-fed rabbits exposed only to CO (6 weeks at 150 to 200 ppm or for 201 to 304 minutes at 2000 to 4000 ppm) showed no evidence of histotoxic effects on intimal/subintimal morphology of coronary arteries or aorta. The weight of evidence suggests that there is doubt as to the relationship between CO exposure and atherosclerosis.

Coronary Blood Flow

Carboxyhemoglobin increases result in an increased coronary blood flow (CBF).[1,9,10,45,116] This increase in CBF as a function of COHb is apparently not sufficient to prevent a reduced O_2 supply even at COHb levels as low as 4 percent.[2] This partly compensatory response is not affected by autonomic nervous system blockage and is not mediated by heart rate,[116] but is apparently due to auto-vasodilatory activity.[2] Increased CBF in response to COHb was no longer observed in atrioventricular-blocked dogs being maintained by a pacemaker.[45]

Hemoglobin

Carbon monoxide apparently induces increases in Hb that, to an unknown extent, compensate for reduced availability of Hb for O_2 carrying. Penney et al.[81,82] showed increased Hb levels in rats exposed to as little as 115 mg/m^3 (100 ppm, 9.2 percent COHb) CO continuously, which began early in the exposure period and reached an asymptotic value by about 30 days of exposure. These results were similar to those reported by Jones et al.[49] in rats, and by Musselman et al.[70] in dogs continuously exposed to 58 mg/m^3 (50 ppm) CO for 3 months. Theodore et al.[99] continuously exposed monkeys and dogs to 460 to 575 mg/m^3 (400 to 500 ppm) CO for 168 days and showed increased Hb levels that reached asymptotic values at about 30 days but which began to decline toward control values at about 140 days. This might represent a failure of the compensatory Hb increases after very long exposures, but further study is needed to support such a conclusion. Jaeger and McGrath[47] exposed Japanese quail to 345 to 403 mg/m^3 (300 to 350 ppm, 30 percent COHb) CO for 28 days and observed increased hematocrit, Hb, plasma volume, and blood volume. They also noted right ventricle hypertrophy. Baker and Tumasonis[11] reported vascular hypertrophy in chick embryos after 18-day exposure of eggs to 490 mg/m^3 (425 ppm, 6.15 percent COHb) CO.

Apparently, continuous exposure to CO is needed to show increased Hb levels at lower CO exposures. Preziosi et al.[86] using dogs exposed to 58 and 115 mg/m^3 (50 and 100 ppm, 7 to 12 percent COHb) CO on various intermittent schedules for 6 weeks, reported no effects. A group of four dogs exposed to 115 mg/m^3 (100 ppm) continuously for 6 weeks also showed no effects. Stupfel and Bouley,[95] using rats and mice exposed to 58 mg/m^3 (50 ppm) CO intermittently for 2 years, and Eckhart et al.,[32] using monkeys exposed intermittently to 23 and 77.5 mg/m^3 (20 and 67.5 ppm, 2 to 10 percent COHb), did not demonstrate any COHb increases. Gasaskina,[38] Ljublina,[58] and Rylova,[89] using rabbits, guinea pigs, rats, and mice exposed for long periods to 58 mg/m^3 (50 ppm) CO, did not find any blood morphology changes. Kalmaz et al.[50] exposed rabbits to 50 ppm CO for 8 weeks and found no change in Hb concentration. However, they did find increased fibrinolytic activity consequent to the CO exposure. The report may be subject to considerable doubt since their animals, when exposed to ambient air, had COHb levels of approximately 5 percent, and their CO-exposed (50 ppm) animals had extremely high COHb levels--in excess of 30 percent.

Alterations in Hb have been reported for short-term CO exposures as well as long-term studies. Ogawa et al.[75] reported that in dogs a 30-minute exposure to 690 mg/m^3 (600 ppm, 58.2 percent COHb) CO produced a decrease in plasma volume resulting in hemoconcentration. They attributed the plasma decrease to an increase in vascular permeability. Syvertsen and Harris,[97] using 224 mg/m^3 (195 ppm) CO for 72 hours (30 percent COHb), also reported increased Hb but attributed their findings to increased erythropoiesis. The latter study, which used intermediate durations of exposure, probably suggests early Hb compensation similar to the long-term findings.

Summary and Conclusion of Studies on CO's Effects on Cardiovascular System in Experimental Animals

Table 10-2 shows a summary of all of the reviewed studies pertinent to experimental animals and cardiovascular systems. From these data it may be concluded that under most circumstances EKG abnormalities may be noticed after relatively long-term intermittent exposure to 115 mg/m^3 (100 ppm, 8 to 13 percent COHb) CO and sometimes, depending upon the species, exposure regimen, etc., as low as 58 mg/m^3 (50 ppm, 4 to 7 percent COHb) CO. Various signs of cardiac damage are found at similar levels.

Decreased thresholds to electrically induced fibrillation have been demonstrated at CO levels as low as 115 mg/m^3 (100 ppm, 6 to 12 percent COHb) CO in exposures as short as 2 hours, but these findings are not universal. It is almost universally demonstrated that when experimental animals are fed high cholesterol diets, they develop increased coronary atherosclerotic damage if they are exposed to CO levels as low as 115 to 230 mg/m^3 (100 to 200 ppm, 9 to 18 percent COHb). These exposures were made on long-term, intermittent schedules. Similar findings of increased damage in the aorta are in greater dispute but have also been reported with exposures to CO as low as 196 mg/m^3 (170 ppm, 17 percent COHb). Apparently, such damage and perhaps other atherosclerotic effects are attributable to CO-induced alterations in serum cholesterol and lactate dehydrogenase alterations.

As reported for CNS structures, coronary blood flow appears to be increased by vasodilation, when CO is present, but this increased flow rate is not sufficient to compensate entirely for the reduced O_2 supply. Needless to say, these findings are not as consistent as might be desired. It is difficult to resolve the disagreement, in most cases, because of differences in exposure regimens, experimental animal species, and analytic techniques, to name but a few of the common problems of comparison.

Despite the problems in the literature and the heterogeneity of reported results, it seems safe to conclude that cardiovascular damage can be demonstrated to occur as a result of long-term, intermittent exposure to CO concentrations as low as 58 to 115 mg/m^3 (50 to 100 ppm). Long-term exposure to continuous low concentrations of CO at 58 to 115 mg/m^3 (50 to 100 ppm) produces increased Hb beginning about 72 hours after exposure and maximizing in about 30 days. Short-term increases in hemoconcentration are apparently the result of reduced plasma volumes. These results contrast with neuro-behavioral data, which were usually collected from short-term exposures and which demonstrated certain functional deficits that occur at CO levels as low as 115 to 230 mg/m^3 (100 to 200 ppm). Studies designed to provide more short-term exposures during cardiovascular tests and more long-term results in neuro-behavioral data are needed.

OTHER DEPENDENT VARIABLES

Feeding, Drinking, and Body Weight

Koob et al.[54] using two strains of rats exposed to 288, 575, and 1150 mg/m^3 (250, 500, and 1000 ppm) CO for 24 hours, showed decreased food and water intake and decreased weight

TABLE 10-2. SUMMARY OF EFFECTS OF CARBON MONOXIDE ON CARDIOVASCULAR SYSTEMS OF ANIMALS

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Lewey and Drabkin,[50] Erich et al.[33]	Dog n = 4-6	100 ppm for 11 wk for 5.75 hr/day	20%	EKG and cardiac pathology	Some subjects showed abnormal EKG, most showed increased heart size, muscle degeneration, necrosis.	
Lindenberg et al.[57]	Dog n = 12	50-100 ppm for 6 wk intermittently or continuously	2.6-5.5%	EKG and pathology	Abnormal EKG, changes in right ventricular and arterial pressures.	
Preziosi et al.[86]	Dog n = 46	50-100 ppm for 6 wk on various daily schedules	7-12%	EKG and pathology	Abnormal EKG, heart dilation, myocardial thinning, some subjects showed scarring and degeneration in heart muscle.	COHb levels were low for exposure levels used.
Musselman et al.[70]	Dog n = 4	50 ppm for 3 mo continuously		EKG, heart rate	No effects.	Very small n.
Thomsen[100]	Cynomolgus monkey n = 20	250 ppm continuously for 2 wk	20.6%	Cardiac pathology	Widening of subendothelial spaces of coronary arteries with accumulation of cells with and without lipid droplets.	Lipid-laden cell findings indicate greater sensitivity of monkeys than of rabbits (22).

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Eckhardt et al.[32]	Cynomolgus monkey n = 27	20 and 67.5 ppm, 22 hr/day for 2 yr	2.5-5% and 4.8-10%	Cardiac fibrosis	No effects.	Unusually wide variation in COHb.
Penney et al.[81,82]	Rat n = 32	100 ppm, 46 days 200 ppm, 30 days 500 ppm, 20-42 days	9.2% 15.8% 41.1%	Heart size	Hypertrophy of both left and right ventricles.	Also studied hypoxic hypoxia and lactate dehydrogenase isozyme.
Stupfel and Bouley[95]	Rat n = 336, mouse n = 767	50 ppm, 95 hr/wk whole natural life expectancy up to 2 yr (also short-term)		EKG, organ weights	No effects.	Also showed no effects on other variables.
Thomsen and Kjeldsen[102]	Rabbit n = 61	50, 100, and 180 ppm for periods ranging from 30 min 24 hr	4.5% 9.0% 17.0%	Aortic damage	Increased focal intimal lesions at 180 ppm, 4 hr.	Conducted blind study.
Kjeldsen et al.[52]	Rabbit n = 16	180 ppm, 2 wk	16.7%	Myocardial ultrastructure	Signs of myocardial damage.	
Thomsen and Kjeldsen[101]	Rabbit n = 42	50, 100, and 180 ppm for 2-48 hr	4.5%, 8.5%, 17.0%	Myocardial ultrastructure	Ultrastructural damage threshold of 100 ppm for 4 hr.	
Tumasonis and Baker[106]	Chick embryo n = 108	425 ppm for 144 and 168 hr	25.4%	Cardiac size	Cardiac hypertrophy.	

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Theodore et al.[99]	Monkey n = 9, baboon n = 3, dog n = 16, rat n = 136, mouse n = 80	400-500 ppm for 168 days	32-38% (dogs and monkeys only)	Cardiovascular damage	No changes except slight hypertrophy in rat heart.	
DeBias et al.[23-25]	Cynomolgus monkey n = 52	100 ppm for 24 wk, 23 hr per day	12.4%	EKG and susceptibility to induced fibrillation	Abnormal EKG and increased sensitivity to fibrillation voltage.	Infarcted animals showed greatest effect of COHb on both dependent variables.
Malinow et al.[60]	Cynomolgus monkey n = 26	500 ppm, 6 min pulses with a 24-min declining washout, pulsed once per hr, 12 hr/day for 14 mo	21.6% at the end of 12 hr. period	EKG and fibrillation threshold	No effects.	Subjects on normal and high cholesterol diets.
Aronow et al.[5]	Dog n = 21	100 ppm, 2 hr	6.3%	Ventricular fibrillation threshold in subjects with acute myocardial injury	Reduced threshold.	Conducted blind study.
Astrup et al.[6]	Rabbit n = 24	170 ppm for 8 wk, then 350 ppm for last 2 wk	17-33%	Cardiovascular pathology	1. Increased aortic atheromatosis and cholesterol. 2. Local degenerative signs and hemorrhages in hearts.	

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Webster et al.[108]	Squirrel monkey n = 22	100-300 ppm 4 hr/day, 5 days/wk for 7 mo using a gradually increasing exposure until 3 mo then reduce to 250 for 4 mo	9-26%	Atherosclerosis in various cardiac structures plus serum cholesterol	Increased coronary atherosclerosis but no effects on serum cholesterol, aortic and carotid atherosclerosis.	Subjects on high cholesterol diets.
Astrup et al.[7]	Rabbit n = 24	Low exposure for 8 wk, higher exposure for last 2 wk	15% and 30%	Aortic cholesterol	Increased in CO exposed groups.	Cholesterol-fed animals.
Davies et al.[22]	Rabbit n = 24	4 hr/day, 7 day/wk, 10 wk	20%	Blood cholesterol and cardiovascular pathology	Increased atherosclerosis in coronary artery but no aortic differences or plasma cholesterol differences.	Study disagrees with Astrup et al.[5]
Malinow et al.[60]	Cynomolgus monkey n = 26	500 ppm, 6 min pulses with a 24 min declining washout, pulsed once per hr, 12 hr/day for 14 mo	21.6% at end of 12 hr period	Aortic and coronary atherosclerosis	No effects.	Subjects on high and low cholesterol diets. Disagrees with Astrup et al.[5]
Stender et al.[94]	Rabbit n = 30	200 ppm continuously or 12 hr/day for 6 wk	17%	Cardiovascular pathology	No differences in atherosclerosis but CO produced higher serum cholesterol levels.	Serum cholesterol was controlled by adjustments of individual diet. Apparently coronary atherosclerosis in (17) was caused by increased serum cholesterol.

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Hellung-Larsen et al.[43]	Rabbit n = 16	170 ppm-550 ppm in ascending levels for 5-11 days	15-35%	Lactate dehydrogenase enzymes (LDH)	LDH increases in aortic arch.	
Penney et al.[81,82]	Rat n = 32	100 ppm, 46 days 200 ppm, 30 days 500 ppm, 20-42 days	9.2% 15.82% 41.12%	LDH	LDH increases resulting from CO exposure.	
Ayres et al.[9,10]	Dog n = 40	50,000 ppm for 30-120 sec and 1000 ppm for 8-15 min		Cerebral blood flow (CBF)	Increased CBF with COHb.	Also studied humans, whose results agree with dogs except dogs were more resistant to COHb below 25%.
Horvath[45]	Dog n = 5-7	Single dose of CO to produce desired COHb (3 levels)	6.2-35.6%	CBF	Increased CBF with COHb.	Atrioventricular blocked dogs, maintained by pacemaker, did not show this effect.
Young and Stone[118]	Dog	1000 ppm until O_2 saturation reduced by 30%		CBF	Increased CBF with COHb even when heart rate paced at 150 beats per min or with blocked autonomic nervous system.	
Adams et al.[2]	Dog n = 10	1500 ppm for 30 min		CBF	CBF increased as linear function of COHb.	CBF increase was not enough to compensate for increased energy expenditure.

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Jones et al.[49]	Rat n = 35, guinea pig n = 35, monkey n = 9, dog n = 6	51, 96 or 200 ppm for 90 days	3.2-6.2% 4.9-12.7% 9.4-20.2% depending upon species	Hemoglobin (Hb) levels	Increases in rats at both exposure levels. Increases in all animals at 200 ppm.	Increased Hb in rats at 96 ppm was larger than at 200 ppm.
Penney et al.[81,82]	Rat n = 32	100 ppm, 46 days 200 ppm, 30 days 500 ppm, 20-42 days	9.20% 15.82% 41.12%	Hb levels	Increased at all levels.	About 30 days until Hb approached asymptotic values.
Theodore et al.[99]	Monkey n = 9, dog n = 16	400-500 ppm continuously for 168 days	32-38%	Hb levels and blood volume	Increased Hb and blood volume, slight decrease toward control values after 140 days.	About 30 days until Hb approached asymptotic values.
Musselman et al.[70]	Dog n = 4	50 ppm continuously for 3 mo		Hb, hematocrit, and red cell counts	Increased.	
Preziosi et al.[86]	Dog n = 46	50 and 100 ppm for 6 weeks on various intermittent daily schedules	7-12%	Hb level	No effects.	
Stupfel and Bouley[95]	Rat n = 336, mouse n = 767	50 ppm for 90 hr/wk up to 2 yr		Hb level	No effects.	

TABLE 10-2 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Eckhardt et al.[32]	Cynomolgus monkey n = 27	20 and 67.5 ppm, 22 hr/day, for 2 yr	2-5.5% and 4.8-10.0%	Hematocrit, Hb and erythrocyte counts	No changes.	Unusually wide variation in COHb.
Ogawa et al.[75]	Dog n = 16	6000 ppm for 30 min	58.2%	Plasma volume	Decreased.	Probably as a result of increased vascular permeability. See Parving et al.[77]
Syvertsen and Harris[97]	Dog n = 12	195 ppm for 72 hr	≃30%	Hematocrit and Hb	Increased concentrations but inferred no increase in plasma volume.	Attributed change to increased erythropoiesis.
Jaeger and McGrath[47]	Quail n = 40	300-350 ppm for 28 days continuous	30%	Hematocrit, Hb, plasma, blood volume, heart size, fasting glucose and carbohydrate stores	Hematocrit, Hb, plasma and blood volumes increased. Right ventricle hypertrophy. Higher fasting glucose muscular carbohydrate.	
Baker and Tumasonis[11]	Chick embryo n = 90	425 ppm during first 18 incubation days	6.15%	Vascular structure, LDH and serum albumin	Vascular hypertrophy, increased LDH and serum albumin.	

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25° C, 760 torr.

gain during the exposure period. Fechter and Annau[34,35] reported slightly lower weight gains in rats whose mothers had been exposed to 174 mg/m^3 (150 ppm, 15 percent COHb) CO during their full terms of pregnancy. Theodore et al.[99] noted no significant body weight effect in rats exposed for 168 days to 460 to 575 mg/m^3 (400 to 500 ppm) CO, but apparently the rats were somewhat more mature than those of Koob et al.[54] No significant weight, feeding, or drinking effects were noted in three other studies: (1) Musselman et al.,[70] using rats, rabbits, and dogs exposed to 58 mg/m^3 (50 ppm) for 3 months; (2) Campbell,[17] who exposed rats to 3450 mg/m^3 (3000 ppm) for a total of 300 days, and (3) Stupfel and Bouley,[90] using rats and mice exposed intermittently for periods ranging from 1 month to 2 years. Since the only study that showed marked effects on weight and intake was a short-term exposure, it is not possible to conclude that weight gain and intake are affected by CO exposure. Possibly these two factors are affected only in the early stages of exposure or only in growing organisms.

Biochemical Effects and Drugs

Pankow et al.[76,79] injected CO subcutaneously in rats to produce COHb levels of 40 to 50 percent and showed that only the higher dosage increased leucine aminopeptidase activity in the liver after a single injection. Forty injections of the dose producing the lower COHb over a period of 53 days also produced an enlarged liver. Martynjuk and Dacenko[62] showed increased aspartate and alanine aminotransferase activity after only 20 mg/m^3 (17 ppm). Kustov et al.[55] exposed rats to 58 mg/m^3 (50 ppm) and observed depressed cytochrome oxidase activity and increased succinate dehydrogenase activity in liver. The latter two studies indicate general hypoxic effects.

Swiecicki[96] exposed rats to CO and noted that an increase in adrenergic system activity produced an increased carbohydrate metabolism. Such metabolic alterations could explain weight changes if such changes were verified.

Montgomery and Rubin[67] exposed rats to 288 to 3450 mg/m^3 (250 to 3000 ppm) CO for 90 minutes in several groups (20 to 60 percent COHb) and then injected two dissimilar drugs (hexobarbital and zoxazolamine). They showed that CO exposure prolonged zoxazolamine effects at 288 mg/m^3 (250 ppm) CO and hexobarbital effects at 1150 mg/m^3 (1000 ppm) CO.

Miscellaneous Variables

Schwetz et al.[90] exposed pregnant rabbits and mice to 288 mg/m^3 (250 ppm) CO for either 7 or 24 hour per day for days 6 to 18 and 6 to 15 of gestation. No statistically significant differences in the number or extent of skeletal birth defects were noted.

Summary and Conclusions of Studies of CO's Effects on Other Dependent Variables in Experimental Animals

Table 10-3 presents a summary of findings regarding CO and various other dependent variables.

The data regarding feeding, drinking, and body weight suggest the possibility of a short-term effect at 288 mg/m^3 (250 ppm) CO levels but definitely show no long-term effects. Since only one study showed short-term weight loss, this finding should be viewed with caution.

TABLE 10-3. SUMMARY OF CO EFFECTS UPON METABOLISM

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Koob et al.[54]	Rat n = 36	250, 500, and 1000 ppm for 24 hr		Food and water intake and weight	Decreased intakes during exposure, less weight gained.	True for 2 strains of rat. Related to catecholamine findings. 200 g starting weight.
Fechter and Annau[34,35]	Rat n = 16-32	150 ppm during full term of pregnancy	15% (maternal)	Body weight of offspring	Nearly same at birth but gained at significantly lower rate.	Body-weights not significantly different until day 4.
Theodore et al.[99]	Rat n = 136	400-500 ppm for 168 days		Body weight	CO group had slightly lower mean but not significant.	240 g starting weight.
Musselman et al.[70]	Rat n = 100, rabbit n = 40, dog n = 4	50 ppm for 3 mo		Body weight	No CO effect.	
Campbell[17]	Rat n = 36-45	Gradually increasing exposure reaching 3000 ppm at 100 days, intermittent exposures		Body weight	Slightly fewer gains during first 100 days and then increased gain in last 200 days.	1. No significance tests and slight differences. 2. First 100 days represented normal rapid growth phase.
Stupfel and Bouley[95]	Rat n = 336, mouse n = 767	50 ppm for 95 hr/wk for natural life up to 2 yr; also 1-3 mo exposure groups		Body weight, food and water intake	No effect due to CO.	

TABLE 10-3 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Pankow and Ponsold[76,77]	Rat n = 20-30	Subcutaneous injection of 7.2 and 9.6 mMol/kg, 40 injections in 53 days	50% 1 hr after injection	Leucine aminopeptidase activity and liver weight	Single 9.6 mMol/kg injection increased enzyme. Repeated 7.6 mMol/kg injections increased enzyme and liver wt.	
Martynjuk and Dacenko[62]	Rat n = 95	17 ppm		Aspartate and alanine aminotransferase activity	Increased during exposure.	
Kustov et al.[55]	Rat n = 92	50 ppm		Cytochrome oxidase and succinate dehydrogenase activity in liver	Depressed cytochrome oxidase; increased succinate dehydrogenase.	
Swiecicki[96]	Rat n = 60	1% for 15 min		Adrenergic system	COHb levels stimulate system.	Increased carbohydrate metabolism.
Pankow and Ponsold,[77] Pankow et al.[78]	Rat n = 110	CO exposure combined with 1% ethanol	40-50%	Leucise aminopeptidase (LAP) and glutamic-pyruvic transaminase activity.	Increased LAP activity; enlarged liver with ethanol dosages.	
Montgomery and Rubin[67]	Rat n = 10-20 per group	250-3000 ppm in various groups for for 90 min	20-60%	Rates of metabolism of hexobarbital and zoxazolamine	Prologed response to hexobarbital at 1000 ppm and to zoxazolamine at 250 ppm.	

TABLE 10-3 (continued)

Reference	Animal	Exposure[a]	COHb	Dependent variable	Results	Comment
Schwetz et al.[90]	Pregnant female Mouse n = 35-48	250 ppm for either 7 or 24 hr/day on days 6-15 of gestation	10-15%	Skeletal malformations in pups	No teratogenic effects due to CO.	
	Pregnant female Rabbit n = 20-21	As above on days 6-18	As above	As above	As above.	

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25°C, 760 mm torr.

Even if verified, short-term (24-hour) alterations in feeding and weight maintenance per se are not particularly serious in an applied sense.

Biochemical findings suggest that enzyme and certain other activities might be measurably altered at extremely low levels of CO exposure. But the implication of these findings for health effects is not clear, since the findings may be merely secondary consequences of known hypoxic effects of CO exposure. By themselves these data do not provide information about health concerns. Taken in combination with other findings, these data might be used as supplementary explanatory results. Extensions and verification of these findings should provide interesting interpretive data.

The findings of slowed drug metabolism might have practical import for persons exposed to CO while under medical treatment with drugs or under the influence of illicit drugs. The findings in this area are only suggestive; thresholds need to be established for a much wider range of drugs and animals.

There is a paucity of data regarding the effects on offspring for other than cardiac or CNS effects. No skeletal birth defects were noted at relatively high levels of CO.

INTERACTIONS WITH OTHER POLLUTANTS, DRUGS, AND OTHER FACTORS

Many materials by themselves at certain exposure levels may have no harmful biological effects until combined with other substances. The effects of CO have been explored in only a preliminary fashion with respect to such interactions. Carbon monoxide exposure frequently occurs in the natural environment in combination with other pollutants, noise, and drugs such as therapeutic drugs or alcohol. Tobacco smoking raises COHb levels but also has other effects which could act in combination with CO.

Other Pollutants

Busey[13] exposed rats for 52 weeks to various concentrations of airborne pollutants (NO_2, SO_2, $CaSO_4$, PbClBr, and CO), the CO levels of interest being 23 and 77 mg/m^3 (20 and 67 ppm). No consistent pulmonary function changes were seen in any of the groups exposed to one of these pollutants alone or in combination with any other single pollutant. Hematological and biochemical measurements remained within normal limits in all groups. A similar study[14] was made on cynomolgus monkeys which were exposed continuously for 104 weeks. The CO concentrations were 22 and 75 mg/m^3 (19 and 65 ppm). Although some effects were observed with the CO and NO_2 combinations, it was reported that no firm conclusion of any interaction was warranted. The combination of SO_2 (26.2 mg/m^3, 10 ppm) and CO (17 ppm, 20 mg/m^3) resulted in a significantly increased osmotic fragility of erythrocytes.

Yamamoto[115] exposed mice and rats to combustion products from gauze-PAN (Polyacrylonitrile) which were analyzed and shown to contain between 920 and 17,020 mg/m^3 (800 and 14,800 ppm) CO and between 209 and 435 ppm hydrocyanic acid (HCN), depending upon the intensities of exposure. He concluded that CO and HCN did not have additive or synergistic effects on survival rates. The effects of CO and cyanogen (CN^-) on the circulation and metabolism of the brain of anesthetized dogs were studied by Pitt et al.[84] Cerebral blood flow increased

130 and 200 percent when COHb levels were 30 and 51 percent. Similar increments in flow were observed when blood CN^- concentrations were 1.0 and 1.5 µg/ml. When CO and CN^- were administered simultaneously, cerebral blood flow increased additively. Cerebral metabolism increased only at the higher levels of COHb and CN^-, but when both substances at the lower levels were presented to the animal, significant decreases in brain O_2 consumption were found.

Murphy[68] demonstrated that COHb was about 5 percent higher after simultaneous exposure to 345 mg/m^3 (300 ppm) CO and 0.75 ppm O_3 than after 345 mg/m^3 (300 ppm) CO alone in mice, guinea pigs, and rats (25 percent vs. 30 percent COHb). Oda et al.[74] did not detect any effect of simultaneous CO and nitric oxide exposures of 460 ppm and 66 ppm, respectively, on the COHb of mice, beyond that expected due to CO alone.

Murray et al.[69] exposed mice and rabbits to 25 and 70 ppm SO_2, respectively and simultaneously, to 288 mg/m^3 (250 ppm) CO. They studied teratogenic effects on offspring and found no reliable defects due to exposure to either or both substances.

Drugs

Surprisingly little systematic work has been done on the interactions of various drugs and CO. Pankow[77,78] observed that ethanol had additive effects on some enzymes in combination with CO if COHb levels exceed 50 percent. McMillan[64] noted that CO attenuated the behavioral effects of d-amphetamine in a systematic dose-dependent way for CO levels as low as 575 mg/m^3 (500 ppm). Montgomery and Rubin[67] showed that the effects of two dissimilar drugs (hexobarbital and zoxazolamine) were prolonged by CO exposure in rats.

Halogenated Hydrocarbons

Polybrominated and polychlorinated biphenyls are converted in vivo to CO[15,88] or stimulate a catabolic process or processes that would produce CO. The production of CO from dichloromethane (CH_2Cl_2) was reported to be mediated by an enzyme present in the microsomal fraction prepared from hepatic tissue.[44] These studies indicated a direct role of cytochrome P-450 in this process. These observations are similar to those reported by others.[3,27] Dogs were exposed for 2 hours to 500, 1000, 2000, and 5000 ppm of CH_2Cl_2.[1] The rise in COHb was logarithmically related to the CH_2Cl_2 exposure concentration. Coronary blood flow increased 20 to 25 percent during all exposures above 573 mg/m^3. Arterial pressure and myocardial contractility (dP/dt) increased with each concentration. Heart rate was not influenced by CH_2Cl_2 exposure but predisposed the heart to arrhythmias. Interestingly, combined exposures to CO and CH_2Cl_2 showed that CH_2Cl_2 had no effect on the physiologic responses due to CO, but CO antagonized the responses due to CH_2Cl_2.

Other Variables

Temperature appears to affect the survival time of newly hatched chicks exposed to 11,500 mg/m^3 (10,000 ppm), with cooler temperatures producing longer survival.[63] No effort was made, however, to determine whether cool temperatures might simply have slowed down physiologic processes. Variables relating to body and/or environmental temperature should be important but have not been systematically studied.

Variables relating to the method for the administration of CO have received little systematic attention. The uptake was shown to be important by Plevova and Frantik[85] who exposed rats to 230 mg/m^3 (200 ppm) for 30 minutes and to 805 mg/m^3 (700 ppm) for 24 hours. Both exposures resulted in 20 percent COHb, but the longer exposure had more effect on motor endurance. This study is not definitive, however, since the 24-hour group would have reached saturation in 2 to 3 hours, thus spending more time at 20 percent COHb.

Conclusions about Interactions

Despite the paucity of data concerning CO and other substances and conditions, there are enough data to indicate that such interactions might well be of importance to health effects. Quite possibly some of the commonly covarying pollutants and some of the commonly used drugs (therapeutic or otherwise) might interact additively or synergistically to make extremely low levels of CO dangerous. This possibility is based not only upon preliminary evidence but is entirely within the scope of reason on theoretical grounds. In view of the potential importance of such work, it is surprising that more studies have not been reported.

MECHANISMS

It has been generally assumed that the manner in which CO produces deleterious effects is by reducing the O_2-carrying capabilities of the blood. This view has been challenged in several ways, although evidence is still very incomplete.

Hypoxic Hypoxia and Carbon Monoxide Hypoxia

If the effects of CO are limited to CO hypoxia, then CO effects should be similar to the effects of hypoxic hypoxia, given that the severity of the two hypoxias could be equalized. It is easy enough to calculate arterial O_2 levels for CO and hypoxic hypoxias and thus equalize exposures at asymptotic CO saturation levels. It must be borne in mind, however, that exposure to atmospheres with low O_2 concentrations produces a rapid reduction in arterial blood O_2, whereas with CO hypoxia the reduction rate is much slower. Attempting to decide the equivalence of the two hypoxias in short-term exposures is not a trivial task. In long-term exposures where the equilibration process is a small proportion of the exposure, equivalences can more easily be made.

Syvertsen and Harris[97] exposed dogs to either simulated altitude (18,000 feet) or to 225 mg/m^3 (195 ppm) CO for 72 hours and showed that Hb and hematocrit rose to nearly the same values by the end of the period. These blood measures rose gradually for the high altitude group, beginning almost immediately, but for the CO group began to rise only after 48 hours. They also showed that erythropoietic levels increased almost immediately for high altitude groups but did not begin to increase until about 24 hours in the CO group. These differences can probably be explained by (1) the differences in the early levels of hypoxia being more extreme in the high altitude groups, and (2) the chemosensory response to the high altitude condition. This is not, therefore, evidence for some non-hypoxic effect of CO. It does, however, appear that compensation for CO effects is not as fast as for hypoxic hypoxia.

Penney et al.[81] exposed groups of rats to 115, 230, and 575 mg/m^3 (100, 200 and 500 ppm) CO and to 18,000 feet simulated altitude for periods of several weeks and showed that high altitude produced mainly increased right ventricle weight, while CO produced overall heart weight increases. The levels of arterial blood O_2 in high altitude subjects, however, would not have produced equivalent exposures, nor were durations of exposure the same; this result is therefore difficult to interpret.

Winston[110] and Winston and Roberts[111,112] showed that pre-exposure of mice to 500 or 1000 ppm CO for 4 hours resulted in a significant decrease in mortality resulting from a 2875 mg/m^3 (2500 ppm) exposure 24 hours later. They also showed that the short pre-exposure did not protect animals against hypoxic hypoxia. Their conclusion was that selective redistribution of blood flow was responsible for their results.[112]

Annau[4] showed that rats exposed for about 2 hours to 1000 ppm at first showed depressed lever-press rates in a behavioral study, but after the fourth day of repeated testing the decrement in behavior began to approach pre-exposure levels. In contrast, a group of rats exposed to 8 percent O_2 (hypoxic hypoxia) for about 2 hours recovered to normal by the second day of repeated testing. This more rapid recovery by hypoxic animals than by CO-exposed animals is at least a control for possible practice effects.

Koob et al.[54] exposed rats for 24 hours to air containing 16, 14, and 10 percent O_2 or to 288, 576, and 1152 mg/m^3 (250, 500, and 1000 ppm) CO. They showed no differences between CO and lowered O_2 groups in feeding, drinking, and weight gain. This result implies that CO has no effects on these variables other than hypoxic effects, but the dependent variables are rather gross measures.

That CO hypoxia and hypoxic hypoxia are similar in terms of survival effects was suggested by Clark and Otis,[18] who showed that adaptation to CO produced increased tolerance of high altitude and vice versa. Wilks et al.[109] reported similar data. It is difficult to evaluate the equivalence of exposures in these studies, however.

Careful effort to equalize hypoxic hypoxia and CO hypoxia were made by Traystman,[104,105] who measured cerebral blood flow in dogs. Since his subjects were held at constant ventilation, the effects of hypoxia-induced hyperventilation were eliminated. His data show that for exposures of up to 40 minutes, with arterial O_2 values ranging from 4 to 17 percent for both hypoxic hypoxia and CO hypoxia, the CO hypoxia reduced cerebrovascular resistance significantly more than did hypoxic hypoxia. The difference between the two forms of hypoxia diminished as the degree of hypoxia diminished. These data suggest that CO produces a more extreme compensatory response than hypoxic hypoxia, if ventilation is controlled.

Annau[4] exposed rats to 14, 12, 10, or 8 percent O_2 in "air" and to 174, 288, 576, or 1152 mg/m^3 (150, 250, 500, and 1000 ppm) CO for daily exposures of 15 to 60 minutes. He showed that brain-stimulation-reinforced responses were affected by both variables in about the same way except for certain temporal effects over the course of several days exposure. Apparently CO-exposed rats recover response rates more slowly than low-O_2 exposed rats. It is unlikely that very much adaptation to CO would have taken place in the course of a few days of short exposures; therefore, this result is difficult to interpret. If replicable, these data imply that CO has some non-hypoxic effect.

Elimination of Hemoglobin

Geyer et al.[39] replaced the blood of rats with artificial blood. Without Hb, these rats survived 17 hours of exposure to 115,000 mg/m^3 (100,000 ppm) CO, which killed controls immediately. These data imply that CO has only hypoxic effects, but detailed assessments of other functions (e.g., behavior) evidently were not conducted.

Most insects do not have Hb and so could be used to assess whether CO has effects independent of its interaction with Hb. Haldane observed that a cockroach was unaffected by 18 days exposure to an environment containing 80 percent CO and 20 percent O_2. Baker and Wright[12] exposed Coccinella septempunctata (the seven-spotted ladybird) and Carausis morosus (the stick insect) to an environment of approximately 80 percent CO and 20 percent O_2. All ladybirds survived 10 days or less of exposure, but longer periods under these conditions hastened death. Ladybirds were less active and ate less food in this environment. Stick insects lived in an ambient atmosphere containing 20 percent CO, 5 percent O_2, and 75 percent air. Growth was arrested, but no deaths occurred before 14 days; all were dead by day 37. In an 80 percent CO, 20 percent O_2 environment, stick insects died between the 2nd and 21st day of exposure. It was postulated that the respiratory chain of enzymes, although not inactivated, were inhibited to such an extent as to interfere with the animals' well-being. These insects also lack myoglobin.

Certain bacteria can live and grow in a 100 percent CO environment.[102] Carbon monoxide-utilizing bacteria may perform an important function in natural aquatic environments and in soil.

Conclusions about Mechanisms

There is some evidence from comparison of CO and hypoxic hypoxia that CO has non-hypoxic effects, but the evidence is only suggestive at this stage and may derive from dose and saturation rate parameters. There is certainly also evidence for CO having only hypoxic effects, but such evidence stems from the measurement of rather gross variables. Although the evidence is difficult to interpret in terms of mammals, insects having no Hb are apparently affected by CO, at least at very high CO levels.

ADAPTATION, HABITUATION, AND/OR COMPENSATORY MECHANISMS

This section will consider whether animals exposed to CO eventually develop some physiological responses that tend to offset the deleterious effects. While there is possibly a temporal continuum in such processes, in this review the term "adaptation" will be used to refer to long-term phenomena, and the term "habituation" will refer to short-term processes. Allusions will be made, where possible, to the physiological chain of events by which adaptation and habituation come about, but extensive reductive explanations will be avoided. The term "compensatory mechanism" will be used to refer to those physiological responses that tend to ameliorate deleterious effects, whether in the long- or short-term case.

Adaptation (Long-Term)

Killick[51] exposed mice to successively higher concentrations of CO, which in a period of 6 to 15 weeks reached levels of 2300 to 3278 mg/m^3 (2000 to 2850 ppm) CO (60 to 70 percent COHb), showing that non-adapted mice exhibited much more extreme symptoms when exposed to such levels. A control group was used by Killick to partially rule out effects of selection of CO-resistant individuals. Clark and Otis[18] exposed mice to gradually increasing CO levels over a period of 14 days until a level of 1380 mg/m^3 (1200 ppm) was reached. When exposed to a simulated altitude of 34,000 feet, survival of the CO-adapted groups was much greater than controls. Similarly Clark and Otis[18] acclimatized mice to a simulated altitude of 18,000 feet and showed that these altitude-adapted mice survived 2875 mg/m^3 (2500 ppm) CO better than controls. Wilks et al.[109] reported similar effects in dogs.

Gorbatow and Noro[37] showed that rats given successive daily short-term exposures could tolerate, without loss of consciousness, longer and longer exposures. Their CO exposure levels were 2,875 to 11,500 mg/m^3 (2,500 to 10,000 ppm). Increases in tolerance to CO began to be evident as early as the fourth or fifth day of exposure and were still occurring as late as the 47th day. Non-exposure for several days eliminated some of the adaptation. Similar results were reported by Zebro et al.[117]

As discussed in the section on hemoglobin, Hb increases in animals exposed to CO after about 48 hours,[97] and continues to increase in the course of continued exposure until about 30 days, depending perhaps upon exposure level. This hemopoietic response to long-term CO exposure is similar to that shown for long-term hypoxic hypoxia, except that it is slower to start and tends to offset CO hypoxic effects.

Most investigators have at least implied that this increased Hb level is the mechanism by which adaptation occurs. Certainly this explanation is reasonable for the studies showing increased survival in groups adapted for several days.

While much has been written about compensatory Hb increases, little has been done to elucidate the extent to which such increases offset deleterious effects of CO. The probability that some adaptation occurs is supported theoretically due to Hb increases, and empirically in the findings of toxicology studies measuring survival time. But adaptation has not been demonstrated for specific health effects other than survival time.

Compensatory increases in Hb are not without deleterious consequences of their own, such as cardiac hypertrophy. The Hb increases are also not entirely compensatory at all CO levels in view of the fact that deleterious effects still occur at some CO levels for many physiological systems. It is possible, however, that without such mechanisms as Hb increases, CO effects would be worse or would occur at a lower threshold.

Habituation (Short-Term)

Arguments have been made for the possibility that there exist short-term compensatory mechanisms for CO exposure. These hypothetical mechanisms have been: (1) based upon physiological evidence, and (2) used to account for certain behavioral findings.

There is certainly physiological evidence for responses that would compensate for the deleterious effects of CO in a very short time span. As discussed in the section on nervous system and behavior, CO exposure has been demonstrated to produce an increased CNS blood supply, which is apparently produced by cerebrovascular dilation. It has also been shown,[28,66,104,118] however, that the tissue Po_2 values for various CNS sites fall in proportion to COHb, despite the increased blood flow. Apparently, the Po_2 values would fall considerably more without the increased blood flow. Although the published graphs of these data do not show very short time intervals, it appears that tissue Po_2 falls immediately and continuously as COHb rises. Although there is no evidence for time delays or for threshold effects in these data, it is noteworthy that only very high CO levels were employed. Thus, the saturation rates were high, and time lags or thresholds would be difficult to detect.

As discussed in the section on cardiovascular effects, as COHb rises, both coronary blood flow and O_2 extraction in the peripheral musculature increase (see Table 10-2). These, too, are compensatory mechanisms, but mechanisms which have been shown to be only partly effective. None of the studies present evidence of time lags or threshold effects, since only terminal or near-asymptotic values were reported.

The behavioral work upon which short-term habituation hypotheses are predicated are mostly human studies, where CO exposure at very low levels or at very early exposure times (well before asymptotic saturation) have shown performance decrements that were not apparent with higher or longer exposures. Depending upon the particular version, the habituation hypothesis holds that there might exist some threshold value of CO below which no compensation would be initiated, or that there might be some time lag in the compensatory mechanism so that the early effects of CO exposures would later subside. The behavioral data to support this contention will be reviewed in the context of human research; in experimental animal studies little behavioral evidence for such thresholds or time lags is extant. Most of the hypotheses about compensatory mechanisms were based, however, upon post hoc reasoning to explain empirical findings, not upon results from experiments to test the existence or nature of such mechanisms. Disregarding hypothesized time lags and thresholds, without the compensatory mechanisms CO would apparently have even more deleterious effects and the threshold for such effects would be lower.

SUBJECTS AT SPECIAL RISK

From the foregoing review and from additional data reviewed below, it may be inferred that there are sub-groups in the general population of experimental animal subjects that are especially sensitive to the deleterious effects of CO exposure. In some cases studies have been designed to test the specific question of special-risk subjects; in other instances deductions regarding this question have been based upon extant data or theory.

Fetus and Uterine Exposure

Several studies[29,31,34,35,90] have exposed pregnant female animals to CO and in general have shown that the mothers have not been deleteriously affected, while the offspring were. In many cases the deleterious effects in the offspring have disappeared by adulthood, but the indication of deleterious effects during childhood is of concern. Additionally, impairment during maturation can have effects on the normal development of learning and social behavior. Most of the studies cited above did not measure COHb in the fetus during long-term exposure.

Longo and Hill[59] studied the uptake and elimination of CO in fetal and maternal sheep. Following exposure to 58 mg/m^3 (50 ppm) CO, steady-state maternal COHb was 7.2 percent and fetal COHb was 11.3 percent, while exposure to 115 mg/m^3 (100 ppm) resulted in steady-state COHb concentrations of 12.2 and 19.8 percent in mothers and fetuses, respectively. The increase in maternal COHb resembled a simple exponential process with a half-time of 1.5 hours. The half-time for the fetus was 5 hours. The decay curve for CO elimination showed similar relations, with fetal washout occurring slower than in the mother.

The data of Longo and Hill[59] on long-term maternal exposures suggest that the fetus is at special risk because of higher COHb levels than those of the mother. Two studies using short-term exposures[29] also measured COHb in the fetus and showed that it was much lower in the fetus than in the mother, probably because of slower COHb rise times. Since short-term exposures also adversely affected the fetus, these studies imply that not only is the fetus' COHb higher than the mothers' for long-term exposures, but that the fetus is apparently more fragile and more subject to CO effects even if COHb is controlled.

While the data clearly show that fetuses are especially at risk, much more information is required regarding dose-response functions, from which thresholds, extent of effects, and interactions with other factors may be estimated.

Impaired Groups

There is clear evidence that subjects with impaired cardiovascular functioning are especially sensitive to CO exposure because of the already reduced and/or marginal O_2 supply from the blood. Any additional loss of O_2 due to COHb produces local or general hypoxias and deleterious effects. This has been demonstrated for cardiac damage[5,23-25] and for the effects of high cholesterol levels in some cardiovascular structures.[6,60] These results should hold for central nervous system structures but have not been demonstrated.

Subjects with significant pulmonary function impairment might be at special risk to CO exposure because of the inadequate supply of O_2 to the blood, especially during exercise. Specific data on this subject in experimental animal research are not available.

There is one large group of subjects in which several of the above mentioned impairments are commonly found, i.e., the group including aged individuals. When there is any impairment such as cardiac damage, cholesterol buildup in any vascular structures, anemia and/or pulmonary function impairment, low levels of CO could precipitate major adverse health effects, especially during exercise. Unfortunately, there is no experimental evidence for deleterious CO effects in many of these areas other than cardiovascular impairment. Certainly more data are needed to estimate dose-response curves so that the extent, threshold, and pattern of those problems can be assessed.

Drugs

Alcohol has already been shown to have additive effects with CO,[77,78] albeit at high exposure levels. More refined studies with other dependent variables will very likely show lower-level effects. Sedatives and other drugs are potentiated by CO.[67] Stimulant drugs have been shown to be attenuated by CO;[64] dose-response functions and a wide range of dependent variables are not known.

Unadapted Populations

There is considerable evidence for long-term adaptation to high altitudes in the form of increased Hb levels. Individuals who have not had such adaptation and are then simultaneously exposed to high altitude and high CO concentrations would seem to be at higher risk because of the simultaneous effects of hypoxic hypoxia and CO hypoxia. A great deal of published information is available on these separate factors. Therefore, estimates of threshold and dose-response functions could be obtained by projecting arterial O_2 content from simultaneous hypoxic and CO conditions. This remains to be done.

SUMMARY

From the foregoing studies of low-level CO effects in normal experimental animals, it may be concluded that CO produces deleterious effects mainly upon the cardiovascular systems and the CNS. While many particular conclusions are still in dispute, it seems safe to conclude that cardiovascular effects can be demonstrated with CO exposures as low as 58 mg/m^3 (50 ppm, 4 to 7 percent COHb). Behavioral and CNS effects seem to require a minimum CO exposure of 115 mg/m^3 (100 ppm, 12 to 20 percent COHb) to produce effects.

The particular levels of CO in experimental animal studies are not as important as the generalizations about the variables (dependent, independent, and interactive) that are likely to be important in humans. Such knowledge also permits the prediction of specially sensitive populations and allows for anticipation of new effects not yet observed, and sometimes too dangerous to produce, in humans. The particular level at which such effects become important in man is an empirical matter for human research.

Although thresholds and dose-response functions have been discussed here, there remains a great need to quantify important health effects of CO. Too little is known about interactions with other pollutants, drugs, or other environmental conditions. Much remains to be specified regarding particularly sensitive groups. There is the suggestion that CO has other non-hypoxic effects, which in turn suggest that CO might have as-yet-unanticipated health effects. From this discussion it may be concluded that a great deal more information about CO is required with respect to interactions, groups at special risk, and non-hypoxic CO effects.

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11. EFFECTS OF LOW-LEVEL CARBON MONOXIDE EXPOSURE ON HUMANS

INTRODUCTION

Carbon monoxide (CO) poisoning is a common form of both accidental and intentional poisoning. The early history (from the days of Aristotle) of CO and its effects on mammals has been well described by Lewin.[142] The clinical-pathological effects of CO overdosage, especially of large increments in carboxyhemoglobin (COHb), are adequately documented in several monographs.[32,94,130,142,144,145,219] Neurological signs and sequelae, as well as anatomical alterations in various tissues, are discussed in these reviews, as are the occurrences of CO intoxication, clinical symptomology, complications, progressions, and emergency and subsequent treatment. An extensive bibliography of abstracts up to 1966 was compiled by Cooper.[56] Descriptions of severe effects from exposure to high CO concentrations are not directly germane to the problems from exposure to current ambient levels of CO, but they are valuable in that they indicate the potential effects of accidental overdose.

Extensive studies have been conducted with various animal species as subjects. Under varied experimental protocols, considerable information has been obtained on the toxicity of CO, its effects on blood, tissues, metabolism, etc. The effects observed on experimental animals have provided some insight into the role CO plays in cellular metabolism. However, caution must be exercised in extrapolating the results obtained from these data to man. Not only are there questions related to species differences, but exposure conditions differ markedly in the studies conducted by different investigators.[52]

Research on human beings is especially fraught with methodological problems. As with the literature on experimental animals, many methodological and reporting problems make the data difficult to interpret. These problems include: failure to measure blood COHb levels; failure to distinguish between the physiological effects from a CO dose of high concentration and the slow, insidious increment in COHb over time from lower inhaled CO concentrations; failure to measure the amount of CO brought to or removed from the lungs by changes in alveolar ventilatory volumes; and the use of small numbers of experimental subjects. Other factors involve failure to provide control measures (via double-blind administration) for experimenter bias and experimenter effects; control periods so that task-learning effects do not mask negative results; homogeneity in the subject pool, particularly in groups labeled "smokers;" control of possible boredom and fatigue effects; and poor or inadequate statistical treatments.

An almost universal problem in this area of research is the use of inappropriate statistical techniques for data analysis. Experimenters commonly use tests designed for simple two-group designs when analysis of variance is required, or use several univariate tests when more than one dependent variable is measured and multivariate tests are appropriate. Such inappropriate statistics usually yield results in which the p-value is too small, so that the possibility exists that too many results were falsely declared to be statistically significant. In this review, an effort will be made to account for such problems whenever possible by making appropriate corrections or by discussing the possible consequences of such an error in context.

The above problems are not peculiar to human research data (as discussed in Chapter 10). A problem unique to human research is that only low levels of CO exposure may be safely used. In such instances of low-level exposure, research findings necessarily deal with near-threshold effects. The so-called "threshold" for an effect is conceptually defined as a CO level below which no deleterious effect on the dependent variable occurs and above which an effect is in evidence. In practice, a threshold must be defined as a CO level above which an effect upon a dependent variable is produced a certain percentage of the time it is administered. Usually, a threshold is defined in terms of the point where an effect is noted 50 percent of the time, although many other, possibly better, definitions are in use. When research is necessarily restricted to such barely noticeable effects it may be expected that (1) results will be more variable because of statistical sampling fluctuations and (2) other uncontrolled variables that also affect the dependent variable in question will be of major importance and will increase the variability of results. For these reasons, data on human beings, while being of prime interest, will also be of highest variability. Such high variability must be resolved with (1) large groups of subjects (2) theoretical interpretation of results relying on knowledge gained from experimental animal data, and (3) consideration of consistency of the data within and across experiments.

This chapter is intended to review data from studies in which people have been either accidentally or intentionally exposed to low levels of CO. The summary and conclusion of each section in the chapter integrates the relevant material from studies of experimental animals. Unless otherwise stated, all subjects are considered to be normal (i.e., without debilitating disease).

NERVOUS SYSTEM AND BEHAVIOR

Demonstrable changes in central nervous system (CNS) function in individuals who were inadvertently exposed to high levels of ambient CO in illuminating gas and in automobile exhaust stimulated psychophysiological research. This research attempted to determine psychomotor and psychological aberrations in individuals having lower levels of blood COHb than those observed in CO-poisoned individuals. Early studies in this area suffer from a number of deficiencies. These deficiencies are related to inadequate understanding of the significance of behavioral changes and to inability to distinguish between simple perceptual motor performance and more complex performance involving sustained or selective attention, short-term memory, and decision-making among other possibilities.

Sleep and Activity

O'Donnell et al.[171] sought to determine how overnight exposure to low levels of CO (COHb levels up to 12.6 percent) affected sleep. They found small but unreliable changes that they interpreted as a possible reduction in CNS activation. Groll-Knapp et al.[92] and Haider et al.[102] reported a significant reduction of rapid eye movement (REM) sleep in subjects of both sexes exposed for 7 hours to 115 mg/m^3 (100 ppm) CO.

Vigilance

Vigilance is an individual's ability to detect small changes in his environment that take place at unpredictable times, thus demanding continuous attention for long periods of time. In monotonous tasks, subjects miss signals that they would not have missed when starting the task. Such signals are usually presented visually or aurally.

Fodor and Winneke[71] used an auditory vigilance task in which they presented short bursts (0.36 second) of white noise at 2-second intervals as the stimuli. About three of every hundred of these noises were slightly less intense and were the signal to which the subjects were to respond by pressing a button. Twelve non-smokers (male and female) were tested at 0 to 57 mg/m^3 (0 to 50 ppm) CO for 80 minutes prior to the first of three vigilance experiments. Carboxyhemoglobin was estimated to be 2.3 percent at the beginning and 3.1 percent at the end of the first vigilance test. Subjects were likely to miss more signals during the initial test than during the next two vigilance tests; COHb reached an estimated 4.3 percent at the end of 210 minutes of CO exposure. These data suggested an initial effect, possibly followed by a compensatory response. Compensatory mechanisms might not have been operative during the first test because of either a threshold level of COHb below which no compensatory response would be initiated or a time lag in compensatory responses.

Groll-Knapp et al.[92] exposed subjects to 0, 57, 115, and 172 mg/m^3 (0, 50, 100, and 150 ppm) CO (0.0, 3.0, 5.4, and 7.6 percent COHb) for 2 hours. They used a 90-minute auditory vigilance test which showed a dose-related decrement due to CO; however, their statistical documentation is absent. The same group (Haider et al.[102]) was later unable to replicate the results of this study.[92] Winneke[233] used the same test in studies that involved exposure to 0, 57, 115, and 172 mg/m^3 (0, 50, 100, 150 ppm) CO as well as to methylene chloride (CH_2Cl_2), a compound which causes an elevation in COHb. His results from the CO exposures were negative, in marked contrast to the previous data, despite an estimated COHb level of approximately 9 percent at the end of the 172 mg/m^3 (150 ppm) exposure. He did find that his subjects, as a consequence of CH_2Cl_2 exposure, exhibited a striking decrement in vigilance.

Beard and Grandstaff[23] exposed subjects to 0, 57, 200, or 286 mg/m^3 (0, 50, 175, or 250 ppm) CO (1.8, 5.2, and 7.5 percent COHb estimated from alveolar breath) for 1.5 hours, during which the subjects performed a visual vigilance task. They reported a statistically significant decrement in performance at the two lower CO levels but not at the highest level. Although their statistical procedure is suspect, their data raise again the question of compensatory mechanism thresholds.

Horvath et al.[113] utilized a visual vigilance test and were the only group of earlier investigators to measure COHb. They also required two responses, one for the non-signal stimuli as well as the usual response to the signals. Their subjects were pre-exposed for 1 hour to 0, 29, and 126 mg/m^3 (0, 25, and 110 ppm) CO and then continued the CO exposure during a 1-hour vigilance task. The COHb levels at the beginning of the vigil were 0.9, 1.6, and 2.2 percent, respectively, and at the end of the vigil were 0.9, 2.3, and 6.6 percent. They noted no initial effects of CO, but by the end of the vigil the group exposed to 126 mg/m^3 (110 ppm) showed a statistically significant decrement in performance. Recently Winneke et al.[234] attempted unsuccessfully to replicate the Horvath et al.[113] study. Apparently, however, Winneke et al.[234] provided less sensory deprivation in their study, and this may have raised the arousal level of their subjects, keeping them more alert. Horvath's group[43] also attempted to replicate the earlier study by Horvath et al.[113] They used a less isolated (clear plastic) chamber than in the earlier study and failed to observe a statistically significant decrement due to CO, but their COHb levels were also marginally lower.

Benignus et al.[27] employed a visual numeric monitoring task with subjects exposed to 0, 115, and 229 mg/m^3 (0, 100, and 200 ppm) CO (0, 4.6, and 12.6 percent COHb). None of the CO exposure levels produced any effect on vigilance performance. The task used by Benignus et al.[27] was a fairly complex task with high probabilities of signals. Thus the subjects might have been more aroused than they would have been on a simple vigilance task.

Putz et al.[183] used an auditory and visual monitoring task and exposed subjects to 6, 40, or 80 mg/m^3 (5, 35, or 70 ppm) CO (1, 3, or 5 percent COHb) for 4 hours. Their results showed no CO-related decrements, although they did report electrophysiological effects (to be discussed later). Their signal rates were fairly high, and the performance periods were short. Thus, their subjects might also have been too aroused to show behavioral vigilance decrements.

Krotova and Muzyka[238] studied individuals working for about 2 years in an environment containing CO. They had approximately 4 percent COHb after work. Only 11 of the 56 workers reported a loss of vigilance.

Sensory and Time Discriminations

The first demonstrable influences of CO on CNS functions were noted by McFarland et al.[153] in conjunction with their studies on the effects of altitude and CO on visual thresholds. They observed decrements in visual sensitivity at COHb levels as low as 5 percent. Extrapolation of their dose-response curve implies that impairment would occur at even lower levels. Halperin et al.[104] reported that visual function was impaired at COHb levels as low as 4 percent and that greater impairment occurred at higher COHb levels. They further noted that recovery from the detrimental effects on visual function lagged behind the elimination of CO. McFarland[154] and McFarland et al.[155] were unable to demonstrate statistically significant effects in dark adaptation and glare recovery at COHb levels of 6 to 17 percent. Ramsey[186-187] was unable to demonstrate any CO-induced effect on visual brightness discrimination or depth perception.

Seppanen et al.[205] evaluated the effect of increasing COHb on visual perception and psychomotor performance in smokers and non-smokers. Subjects breathed 1100 ppm carbon monoxide intermittently to eventually reach COHb levels of up to 18 percent. Interspersed between the inhalations of CO were periods during which the subjects were breathing air and tests were performed. No effects on perceptual speed and accuracy were observed. Visual perception as measured by critical flicker fusion frequency was decreased linearly with increasing COHb. This study was unusual in the methods used to increase COHb, i.e., the administration of high CO levels for short duration. The significant findings are therefore difficult to compare to other studies.

A perceptual test and a standard cortical function test, critical flicker fusion frequency (CFFF) apparently is not influenced even by COHb levels of 10 to 12.7 percent.[95,186.187,230,233] Guest et al.[95] also used an auditory analogue of CFFF, the auditory flutter fusion threshold. This threshold was not affected by COHb levels of 10 percent. Grandstaff et al.[90] have recently reviewed these studies.

Studies by Beard and Wertheim[22] suggested an alteration in CNS function because the ability to discriminate slight temporal differences in successive short tones was impaired in subjects having estimated COHb levels of 2 to 3 percent. These data imply an orderly dose-response function with increasing decrements in performance as CO levels increase. Although these data represent the lowest levels of COHb to produce a significant alteration in behavioral performance, questions have been raised as to the validity of the observations. Attempts to replicate these particular findings have been less than satisfactory[171,172,213,210] even though the subjects of all of these other studies attained higher COHb levels. Some of the failures to replicate may be explained on the basis of differing protocols and the environmental conditions under which the tests were conducted. Some investigators designed their experiments to minimize boredom and fatigue while others, conversely, attempted to minimize external influences and conducted their experiments for a relatively long time. Otto et al.,[177] however, made strong efforts to replicate the study accurately and presented a strong rationale indicating that time discrimination is probably not affected at low COHb levels.

Complex Sensorimotor Tasks and Driving

A number of investigators have used broad sensory or motor screening batteries in an effort to discover what types of behavior might be affected by low-level CO exposure. From the standpoint of experimental and statistical design, such studies are not always easy to interpret. When many dependent variables are measured, the chance is increased that one or more of them will be erroneously declared statistically significant. In order to account for this increased probability of an inferential error, more exotic statistical procedures must be used. Such procedures usually involve multivariate techniques or at least conservative corrections. Usually, an increased number of dependent variables requires a concomitantly increased number of subjects. In none of the cases of behavioral screening batteries reported below did researchers take appropriate account of this problem. Therefore, conservative corrections have been applied to the findings discussed below.

Sayers et al.[201] found no significant changes, despite COHb levels of approximately 20 to 30 percent, in hand-eye coordination and steadiness, tapping speed, arithmetic performance (continuous addition), location memory, and simple reaction time tests. Bender et al.[25,26] found a decrement in learning of meaningless syllables and in hand-eye coordination when the COHb levels of his subjects were about 7 percent. Other tests by these investigators failed to show decrements in performance at the same levels of COHb. Schulte[202] exposed firemen to 115 mg/m^3 (100 ppm) CO for variable time periods and reported large changes in performance of a series of complex tasks. In a test where subjects were required to underline all plural nouns in prose passages, decreased performance was noted when COHb was approximately 8 percent. The mean time to complete an arithmetic test significantly increased at similar or slightly lower COHb levels. Schulte may have underestimated the COHb levels, since his subjects, mostly smokers, had initial measured values close to zero. O'Donnell et al.[171] studied the ability of four subjects to perform arithmetic problems without pencil and paper. Their subjects required a longer time to complete the answers (98.64 versus 89.76 seconds when COHb levels were 12.7 and 5.9 percent, respectively). McFarland[154,155] tested subjects' performance of complex psychomotor tasks involving reaction times to central and peripheral stimuli and showed some minimal effects of CO (11 and 17 percent COHb) on attention to peripheral stimuli. Salvatore[199] reported increased reaction times to peripheral stimuli at COHb levels of 4 to 8 percent. Putz et al.[183] reported decrements in hand-eye coordination, response times during a complex monitoring task, and tracking accuracy in subjects exposed to 35 and 70 ppm CO (3 and 5 percent COHb).

Johnson et al.[122,123] studied employees who worked at a U.S.-Mexico border crossing and toll collectors along a toll highway. They believed that more valuable information would be obtained from these workers than from the usual studies on university students. Toll collectors had COHb levels ranging from 1.5 to 11.7 percent, with a mean value of 3.9 percent. The subjects exhibited slowed eye-hand coordination in tasks requiring fine motor control and disruption of performance on two concurrent tasks.

The potential influence on vehicle operators of ambient CO levels, as well as the additional increments in blood COHb levels, has received minimal attention. Suggestive but not conclusive evidence has been reported indicating that drivers in fatal accidents have higher levels of COHb.[236] In the early studies of Forbes et al.,[74] five subjects were exposed to sufficient CO to raise COHb levels as high as 30 percent; and their reaction times, coordination, and perceptual skill were determined within the context of a driving skill test. The subjects showed no effects on skill. Wright et al.[235] used a driving simulator with both smokers and non-smokers as subjects (final COHb levels were 5.6 and 7.0 percent, respectively). They suggested that a 3.4 percent increase in COHb was sufficient to interfere with safe driving. McFarland et al.[154,155] studied subjects actually driving instrumented automobiles under highway conditions while exposed to CO concentrations producing 17 percent COHb. They concluded that such COHb levels do not seriously affect driving, but they did show statistically significant increases in roadway viewing time, though no differences occurred in steering wheel corrections. Preliminary data from Rockwell and others,[191,193,194,231] in studies in which subjects drove instrumented automobiles while exposed to CO levels producing 0, 6, and 13 percent COHb, imply that at COHb levels of 6 and 13 percent subjects showed increased variations in automobile speed, decreased ability to maintain fixed following distances, and decreased steering motions. Rummo and Sarlanis[197] reported that during a 2-hour driving-simulator vigilance task subjects with 6 to 8 percent COHb were significantly slower in responding to changes in speed by a lead car.

Central Nervous System Electrical Activity

Dinman[59] analyzed evoked photic responses in subjects with 22 and 37 percent COHb and found no changes in latency or voltage following photic stimulation. Hosko[112] reported changes in CO-induced visual evoked response, but only at COHb levels of about 20 percent. Putz et al.[183] reported an increase in the amplitude of auditory evoked potentials for CO levels of 40 and 80 mg/m^3 (35 and 70 ppm) CO (3 and 5 percent COHb). Groll-Knapp[92] measured slow-wave brain potentials (the so-called contingent negative variation, or CNV) and noted a diminution in the voltage reached by the CNV and the extent of the drop seen after response stimulus given consequent to CO exposure of 172 mg/m^3 (150 ppm). Otto et al.,[176] in a preliminary report of evoked slow potentials during vigilance performance at 115 and 229 mg/m^3 (100 and 200 ppm) CO (4.6 and 12 percent COHb), showed that CNV amplitude decreased as reported by Groll-Knapp[92] and showed that a positive potential with a latency of about 100 msec increased in amplitude with CO.

Ikuta[118] evaluated 87 male adults who had suffered from CO poisoning at an accidental explosion in a coal mine. Older individuals showed the greatest degree of impairment in somatosensory evoked responses.

Conclusions and Discussion of Nervous System and Behavior in Humans

Table 11-1 shows a summary of research results about the effects of CO on behavior and the central nervous system.

Experimental animal data point toward disturbed sleep patterns, which have also been reported in people at levels of 115 mg/m^3 (100 ppm) CO. General activity levels in humans have not been specifically studied.

Effects of CO on vigilance are in considerable dispute; but some evidence suggests that, if relevant variables are controlled, there is a decrement in vigilance due to CO at a threshold level of about 4 to 6 percent COHb. Human and animal studies point toward such factors as arousal, environmental temperature and humidity, CO dose rate, task variables, and subject cerebrovascular health as important and usually uncontrolled variables. Research will be required to clear up this confusion.

Apparently, visual system impairment at low illumination levels or at quickly-changing illumination is affected by CO exposure at levels approaching zero in a dose-related manner,

TABLE 11-1. SUMMARY OF DATA ON EFFECTS OF CO ON HUMAN BEHAVIOR AND CNS

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
O'Donnell et al.[171]	4	9 hr to 75 and 150 ppm during sleep	5.9% 12.7%	Sleep	No changes large enough to be significant but trends toward deeper sleep with CO.	
Groll-Knapp et al.[93]	10	7 hr to 100 ppm (2nd experiment)		Sleep stages	Altered proportion of sleep stages.	
Haider et al.[102]	20	2-7 hr (50-150 ppm)	3%-12%	EEG in sleeping	REM and stage 2 sleep depressed but greater amount of deep sleep.	
Fodor and Winneke[71]		5 hr (50 ppm)	2-5%	Vigilance	Vigilance at first decreased, then increased.	
Groll-Knapp et al.[92]	20	2 hr (50-100 ppm)	3-7.6%	Auditory vigilance	Decreased vigilance performance.	
Beard and Grandstaff[23]	9	90 min (50, 175 & 250 ppm)	1.8-7.5%	Visual vigilance	Significant reduction in vigilance.	
Horvath et al.[113]	10	1 - 2 1/2 hr (26 and 111 ppm)	2.3 and 6.6%	Visual vigilance	Signal identification performance deteriorated and monotony effect was potentiated.	
Winneke[233]	18	5 hr (50 and 100 PPM)	5.1 and 10% respectively	Vigilance, visual CFFF, and psychomotor tasks comparing effects of CO and methylene chloride	No impairment of performance due to CO exposure could be demonstrated, while CNS depression was shown after exposure to methylene chloride for only 3-4 hours at concentrations as low as 300 ppm.	

TABLE 11-1 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Benignus and Otto[27]	52	3 1/3 hr (100 + 200 ppm)	4.61-12.62%	Vigilance performance (numeric monitoring task)	No effect on vigilance performance.	
Putz et al.[183]	30	4 hr (5-70 ppm)	1-5%	Auditory and visual monitoring	No effects.	
McFarland et al.[153]		4 hr (concentrations high enough to achieve stated COHb levels)	0-11%	Visual sensitivity	Low COHb levels were found to reduce visual sensitivity.	
Halperin[104]	4	3-4 hr (at concentrations high enough to achieve COHb levels stated)	3-6.2%	Visual sensitivity to differences in light intensity	Reduced sensitivity Recovery from effects of CO lags behind elimination of CO from the blood.	
McFarland[154] and McFarland et al.[155]		Exposure time sufficient to achieve stated blood concentrations (700 ppm)	6-17%	Dark adaptation and glare recovery	No statistically significant effects were demonstrated.	
Ramsey[186]	20	45 min (300 ppm)	11.28-15.66%	Brightness discrimination depth perception and CFF	No significant effects demonstrated.	
Weber et al.[230]	20	3.5 hr (150 ppm)	9-11%	Critical flicker fusion frequency	Exposure did not affect CFFF either in monotonous or activating situation.	

TABLE 11-1 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Guest et al.[95]	8	65 min (concentrations high enough to achieve stated blood level)	10%	Auditory flutter fusion threshold and critical flicker fusion frequency with phenobarbitone	No significant effects demonstrated.	
Winneke[233]	18	5 hr (50 and 100 ppm)	5.1 and 10% respectively	CFF	No impairment could be detected due to CO exposure.	
Beard and Wertheim[22]	18	2 1/2 hr (50-250 ppm)	Estimated 2-3%	Discrimination of short intervals of time	Performance deteriorated increasingly with progressively higher concentrations.	
O'Donnell et al.[171,172]	4	9 hr (75 and 150 ppm)	5.9% and 12.7%	Time discrimination	No effects.	Not precise replications of Beard and Wertheim.
Stewart et al.[213,210]	18	4-7 hr (25-100 ppm)		Time discrimination	No effects.	Not precise replications of Beard and Wertheim.
Otto et al.[177]	13	3 hr (0, 75 and 150 ppm)	.16, 3.8 and 7.8%	Time discrimination	No effects.	
Bender et al.[26]	42	3.5 hr (100 ppm)	3.8-8.2%	Level of activation, visual perception, psychomotor performance, learning and retention, Amthauer's I.S.T., subjective condition	Level of activation and IST showed no difference. Performance declined in visual perception, learning and memory and in psychomotor testing.	

TABLE 11-1 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
O'Donnell et al.[171]	4	9 hr (75 and 150 ppm)	5.9% and 12.7%	Mental arithmetic	No effects.	
Bender et al.[25]	42	2 1/2-8 hr (100 ppm)	7.2%-11.6%	Visual perception ability to learn, manual dexterity	Visual perception was not affected, manual dexterity was diminished, learning performance deteriorated.	
McFarland[154] and McFarland et al.[155]	9	Until COHb level achieved (700 ppm)	6-17%	Complex psychomotor tasks	Only "minimal" effects.	
Salvatore[199]	6	20 min (800 ppm)	4-8%	Visual function performance	Detection time was significantly increased. No other effects were noted.	
Putz et al.[183]	(not given)	(not given)	(not given)	Hand-eye coordination, complex monitoring, tracking	Decrements in all measures.	
Johnson et al.[122]	6	8 hr (22.8 ppm) TWA	1.5-11.7%	Eye-hand coordination, time estimation, visual perception, complex arithmetic, choice reaction time, CFF, task time sharing	Eye-hand coordination was impaired. Performance on two concurrent tasks was disrupted.	

TABLE 11-1 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Johnson et al.[123]	10	8 hr (0-41 ppm)	1.66-2.5%	Mental arithmetic, audio digit monitoring, hearing acuity, divided attention, choice reaction time, CFFF, eye-hand coordination, subjective feelings	Hearing acuity and CFF were decreased. Choice reaction time was increased. No difference was noted due to CO in mental arithmetic, divided attention, digit monitoring and subjective feelings.	
Forbes et al.[74]	5	1 hr (90 ppm)	22.4-47.2%	Reaction time, depth perception, visual perception, motor performance in driving	No impairment of function up to 30% COHb.	Poor control data.
Wright et al.[235]	50	Duration of exposure sufficient to raise COHb levels by 3.4% (20,000 ppm)	1.24-6.97%	Simulated driving performance	Impairment of varying degrees.	Poor analysis of results.
McFarland[154] and McFarland et al.[155]	9	Sufficient exposure (at 700 ppm) to produce COHb	6-17%	Driving performance	No effects.	
Ray and Rockwell[191] Rockwell and Weir[194]	3	4-6 hr (950 or 1900 ppm given every 35 minutes in quantities sufficient to maintain COHb levels of 10 or 20% respectively	10 and 20%	Driving tasks	Increased response time to distance and velocity, decreases in time estimation, decrease in driving precision.	Only preliminary analyses.

TABLE 11-1 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Weir and Rockwell[231]	6-12 (for various tests)	90 and 120 min (100 and and 490 ppm respectively)	7-20%	Mean velocity and velocity variance, gas and brake pedal actuations, steering wheel reversals, headway, visual behavior	No performance decrement with normal driving tasks.	
Rummo and Salarnis[197]	7	20 min (800 ppm)	6-8%	Reaction time to speed changes, steering reversal responses	Significant increase in reaction time and fewer steering wheel reversal responses.	
Hosko[117]	12	0.5-24 hr (1-1000 ppm)	Max. 33%	Visual evoked response (VER)	VER alterations associated with COHb levels of 20-22%.	
Putz et al.[183]	30	(not given)	(not given)	Auditory evoked potential	Increased amplitude.	
Groll-Knapp et al.[92]	20	2 hr (50, 100 and 150 ppm)	3-7.6%	Computer analyzed brain potentials	CNV amplitude reduced proportional to progressively higher COHb concentrations.	No significant test data.
Otto et al.[176]	28	2.5 hr (100 and 200 ppm)	4.95 and 12.04%	Event-related potentials	CNV decreased, P100 increased.	Preliminary data.
Ikuta[118]	87	(unknown)	(unknown)	Somatosensory evoked responses	Impaired amplitude	Data obtained 3 years after a coal mine explosion.

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25^{o}C, 760 torr.

but these data are old and should be replicated. Other sensory systems could also be affected but have not been extensively studied. Time discrimination does not seem to be affected by low CO levels.

Complex tasks involving heavy demands upon the subject's attention or fine discrimination are usually not affected by CO, especially if the duration of the task performance is short; however, the data by Putz et al.[183] appear to show such effects. Vigilance and sensory functions, which are certainly components of more complex tasks such as driving, appear to be affected; thus one would expect an effect on the overall task. It is probable that research in both experimental animals and man has not shown reliable effects because: (1) the tasks have functionally overlapping components, so that a great impairment is required before decrements are noticed; (2) performance measures of end-result behavior are sometimes gross and insensitive; and/or (3) the tasks' components stimulate the subject with their variety and thereby keep alertness high. More sophisticated studies are required.

Quantification of electrical activity of the CNS as affected by CO has just begun. While alterations have been demonstrated in both experimental animals and man, interpretation of these results still rests on their correlation with behavioral data because of the lack of general theoretical data about CNS electrical activity.

CARDIOVASCULAR SYSTEMS

Experimental animal studies have suggested that one of the principle effects of CO occurs in the cardiovascular system. This section reviews cardiovascular data from studies of both healthy and impaired human subjects exposed to CO.

Cardiovascular Damage and EKG Abnormalities

Corya et al.[54] presented the first evidence for left ventricular abnormality in five cases of non-fatal CO poisoning (20 percent COHb). Abnormal left ventricular wall motion was shown by echocardiograph in three of five cases. A similar number showed mitral valve prolapse.

Zenkevic[237] conducted clinical and physiological hemodynamic studies on two groups of subjects: individuals in constant contact with CO and individuals having no evidence of chronic CO intoxication. He noted considerable cardiovascular abnormalities in the CO-exposed group. A study of cast-iron workers by Ejam-Berdyev[62] also suggested a larger frequency of cardiovascular as well as CNS disturbances, that was related to the increased blood COHb content of these workers.

Hemp processing in Japanese villages is conducted in small rooms heated by charcoal. Ambient CO concentrations average about 80 mg/m^3 (70 ppm) and reach peak levels of about 344 mg/m^3 (300 ppm). The incidence of myocardosis has been found to be excessively high. Deaths from cardiac failure in these villages have been noted to be 6.8 times greater than the anticipated numbers for the Japanese population.[132]

Only one study has been reported on patients having peripheral vascular disease.[8] Ten men with angiographically documented occlusive arterial disease were exercised on a bicycle ergometer until leg pain occurred. These patients then breathed filtered air 0 or 57 mg/m^3 (0 or 50 ppm) CO for a 2-hour period. Exercise after this time showed that COHb levels of about 2.8 percent significantly decreased the time to onset of pain compared to controls. Alexieva and Simitrova[1] studied a large group of workers exposed to an ambient CO level of 57 mg/m^3 (50 ppm) and reported changes in peripheral vessels that suggested impaired vascular tone.

Bogusz et al.[29] related pathological electrocardiograms, increases in blood lactate levels, and aspartate aminotransferase activity to levels of COHb. Gorski[88] utilized the ballistocardiograph to demonstrate hypoxemia of the myocardium in similar cases. Goldsmith and Aronow[83] have reviewed the available evidence relating CO exposure to the rate of development of arteriosclerotic heart disease (ASHD).

Blood Flow and Related Variables

The heart has a specialized circulatory system in which the primary response to increased metabolic demands can only be secured by an increased cardiac blood flow. Even under no-stress conditions (rest), there is an almost complete extraction, roughly 75 to 80 percent, of the available O_2 supply from the blood. The capacity of increased flow rate to compensate for the small benefit obtainable from more complete O_2 extraction has been shown to be on the order of several hundred percent.

The studies of Ayres et al.[18,19] on the hemodynamic and respiratory responses of man were made during diagnostic cardiac catheterizations. Subjects were given a fixed amount of CO, either 1145 mg/m^3 (1000 ppm) for 8 to 15 minutes or 5725 mg/m^3 (5000 ppm) for 30 to 45 seconds. These procedures induced COHb levels of 6 to 12 percent. Two groups of patients, those with and those without coronary heart disease (CHD), were studied. Normal individuals responded to the presence of elevated COHb by increasing their cardiac output and minute ventilation, but with a decrease in arterial oxygen partial pressure (P_{O_2}). Increased extraction of O_2 from arterial blood occurred, as evidenced by the increased extraction rates. Mixed venous P_{O_2} decreased from 39 to 31 torr, probably as a result of the left shift of the O_2 dissociation curve; arterial P_{O_2} also decreased. These changes were similar at both levels of COHb. In contrast to normal subjects, patients with coronary heart disease (CHD) did not show an increase in cardiac output. Coronary blood flow (CBF) increased significantly in all patients given 5725 $\mu g/m^3$ (5000 ppm) CO for 30 to 95 seconds (COHb about 9 percent), but it only increased in the CHD patients when they breathed 1145 mg/m^3 (1000 ppm) CO for 8 to 15 minutes (COHb about 12 percent). It should be noted that most of these individuals had relatively high initial COHb concentrations. The myocardial arteriovenous O_2 difference decreased in both situations, with the greatest percent decrease occurring at the lowest COHb concentration. In all but two of those patients, coronary sinus P_{O_2} decreased, suggesting that the increase in CBF was insufficient to compensate for the decreased O_2 delivery caused by the presence of COHb. Further evidence of anaerobic myocardial metabolism was suggested by the decreased lactate extraction, with four patients showing lactate production by the myocardium and no lactate extraction. Ayres reported similar changes in concurrent studies conducted on dogs.[18,19] These observations on man suggest that CO inhalation would have a significant effect on arterial P_{O_2} in patients with lung disease as well as certain cardiovascular disorders.

The potential toxicity of CO present in transfused blood has received little attention. Kandall et al.[129] measured COHb concentrations in donor blood and in relatively healthy infants receiving exchange blood transfusions. The mean pre-transfusion COHb in six cases was 1.34 percent. Donor blood contained 5.17 percent COHb, resulting in a mean value of 4.92 percent COHb in the transfused infant. In one infant transfused with blood containing 8.87 percent COHb, the resultant COHb value was 7.43 percent. Although it was stated that the infants did not appear to be adversely affected by the COHb levels reached during exchange transfusion, it should be noted that although measures were gross, adverse effects at these levels of COHb have been observed (see Table 11-9). Furthermore, in individuals whose O_2 transport system or cardiovascular reserve is already compromised, the presence of additional COHb from transfused blood may result in a further and more potentially dangerous decrement in arterial, mixed venous, and coronary sinus O_2 tensions. It should be noted that some blood samples collected from donors had COHb values that exceeded 18 percent.

An additional hazard to patients, especially those undergoing cardiovascular surgery, may develop during anesthesia. Middleton et al.[159] have reported markedly elevated expired CO levels in patients undergoing cardiac bypass surgery. This increment could be related in part to the CO present in transfused blood and/or to the closed-circuit method of anesthesia, which precludes the loss of endogenously produced CO.

Angina

Two groups of investigators[2,6,7] reported studies on patients with angina pectoris. Aronow et al.[6] studied the influence of riding in an open car on a major Los Angeles freeway. Two trips of 90 minutes' duration were made: on one the patients breathed compressed CO-free air, and on the other the ambient CO concentration averaged 61 mg/m^3 (53 ppm). Carboxyhemoglobin levels after the CO-free ride averaged 0.65 percent, in contrast to the 5.08 percent observed after the ambient exposure in the open car. Exercise time on a bicycle ergometer to the onset of angina was determined prior to and after completion of the above exposures. Although no changes in time of exercise to onset of anginal pain were noted after the subjects breathed compressed air, a significant reduction from a mean time of 249 to 174 seconds was found when COHb was elevated. Ischemic ST-segment depression of at least 1 mm after exercise-induced angina pectoris occurred earlier, after less exercise.

Anderson et al.[2] conducted a study in which patients with stable angina walked on a treadmill. They then breathed, while at rest, air containing 57 or 114 mg/m^3 (50 or 100 ppm) intermittently over a period of 4-hours, raising their COHb levels to 2.9 and 4.5 percent, respectively. The repeat exercise tests clearly demonstrated a reduction in walking time to onset of angina. No differences in time of angina onset were observed at the two induced COHb levels, although the duration of pain was longer at the higher COHb levels. Five of the 10 patients had deeper ST-segment depression after CO exposure. Other measures of cardiac function (systolic time intervals, left ventricular ejection time, pre-ejection period index, and pre-ejection peak to ejection time ratio) remained within normal limits.

Another study, by Aronow and Isbell,[7] was somewhat similar to the work performed by Anderson et al.[2] Aronow and Isbell[7] exposed patients (non-smokers at the time of the test) to 57 mg/m^3 (50 ppm) CO, resulting in a COHb concentration of 2.68 percent. This study was conducted as a double-blind random-trial experiment in which subjects breathed CO on two days and compressed CO-free air on two other days. All patients had their angina pectoris documented by history and coronary angiography. A 16 percent reduction in exercise time (bicycle) resulted following the CO exposures. Ischemic ST-segment depression after exercise-induced angina occurred earlier after less exercise and at a lower product of systolic blood pressure times heart rate at the onset of angina after the patients breathed CO. Plotting of the data suggests that there was a linear relationship between COHb levels and the decrease in time to angina. Table 11-2 summarizes the above data.

TABLE 11-2. EXERCISE-INDUCED ANGINA AND CARBON MONOXIDE
(Each Study had 10 Subjects)

Investigator	Carboxyhemoglobin percent		Ambient CO (mg/m^3)	Angina response
	Initial	Final		
Aronow et al.[6]	1.12	5.08	61*	Earlier onset
Aronow and Isbell[7]	1.07	2.68	57**	Earlier onset
Anderson et al.[2]	1.40	2.90	57***	Earlier onset

* Freeway trip
** Continuous exposure for 2 hours in laboratory
*** Intermittent exposure for 4 hours in laboratory

Aronow[12] has recently reported that patients with exercise-induced angina had a lower tolerance to exercise when COHb levels were 1.77 and 2.28 percent. These two blood levels of COHb were found in patients as they sat in ventilated or unventilated rooms with other individuals who were smoking cigarettes. It is possible that in addition to carbon monoxide and nicotine, other components of tobacco smoke, including oxides of nitrogen and hydrogen cyanide, and possibly psychological factors may have contributed to the decrease in exercise performance.

Epidemiological Evidence

Epidemiologic studies[47,81,110] in the Los Angeles area have suggested the possibility of increased mortality from myocardial infarction associated with high atmospheric levels of CO.

There has been some difference of opinion about interpretation of these data. A study similar in design has been completed in Baltimore.[138] The Baltimore data indicate no apparent relation between either the incidence of myocardial infarction or sudden death due to ASHD and the average 24-hour ambient CO concentrations. Neither group of investigators was able to detect any relation between postmortem COHb levels and causes of sudden death. The Baltimore study was superior in that the diagnoses of disease state were more precise and the population base more clearly defined than in the other studies. The ambient levels of CO in Baltimore appeared to be considerably lower than those reported for Los Angeles County.[110] During a 92-day period of seasonally excessive ambient CO, Kurt et al.[139] identified cardiorespiratory complaints (CRC) of a non-traumatic origin from a total of 8556 patient encounters at the Emergency Room of Colorado General Hospital. Excessive numbers of CRC were seen above a threshold limit of 6 mg/m^3 (5 ppm) for the 24-hour mean and for the 13 mg/m^3 (11 ppm) 1-hour mean maximum ambient CO level. Whether this incidence is partially related to the high altitude at which these observations were made needs further investigation.

Radford[184] evaluated patients admitted to the myocardial infarction research unit at Johns Hopkins Hospital. While their diagnoses were consistent with both an acute and chronic effect on the myocardium of long term exposure to CO, the effects observed could not be clearly related to that factor. Therefore, the possibility of an association between CO levels in ambient air and incidence of myocardial infarction or sudden deaths remains in question. It is apparent that more comprehensive and extensive epidemiological studies need to be conducted in order to clarify this issue.

Conclusions and Discussion

Table 11-3 summarizes the data on cardiovascular effects of CO exposure. While the data are extremely limited because of the lack of research on human exposures, it is possible that cardiac damage may result from chronic exposure to CO at levels as low as 80 mg/m^3 (70 ppm). Since more extensive data from animal studies show that such damage is systematically observed in chronic exposures, the results of human studies are not unexpected. The precise threshold level for cardiac damage in humans has not been reliably determined, however, inasmuch as only one study reports a level as low as 80 mg/m^3 (70 ppm).

Certainly the alterations in blood flow observed in man match with those observed in experimental animals. Human cardiac pathology data have been reported, however, that show compensatory changes not occurring as readily or extensively as in animals.

The limited studies on patients having cardiovascular disease suggest that the critical level of COHb is 2.5 to 3.0 percent. Additional and confirmatory studies are definitely needed to determine the lowest concentration of COHb at which no alterations in performance can be detected. The available studies on patients do not give much information about the role of CO in the development of the disease but do give some indication of their dose-response relationship. The validity of these data is strongly reinforced by complementary experimental animal studies that show very similar dose-response curves.

TABLE 11-3. SUMMARY OF DATA ON EFFECTS OF CO ON HUMAN CARDIOVASCULAR SYSTEM

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Corya et al.[54]	5	(unknown)	16-25%	Echocardiographic findings after acute CO poisoning	Echocardiographic (ECG) findings in 4 of the 5 cases indicated prolapse of the mitral valve, suggesting that myocardial damage may occur in cases of non-fatal CO poisoning.	Patients were admitted to a hospital the same day they suffered acute CO poisoning due to a faulty water heater.
Aronow et al.[8]	10	2 hr (50 ppm)	2.77%	Symptoms of intermittent claudication	Intermittent claudication was significantly aggravated due to CO exposure.	
Alexieva and Simitrova[1]						
Bogusz et al.[29]	47	1.33 hr (mean) or 5.5 hr (mean)	average 35% average 17%	Aspartate aminotransferase (AspAT), lactic acid dehydrogenase activity, and lactate level in lighting-gas compared to coal-stove poisonings	Enzymatic changes increase with length of exposure. Changes enzyme activity and lactate level parallel ECG and clinical changes AspAT activity was increased even without ECG or clinical changes.	
Ayres et al.[18]	26	8-15 min (1000 ppm) 30-45 sec (5000 ppm)	mean 8.96%	Systemic and myocardial hemodynamic responses	Coronary blood flow increased, and extraction ratios decreased. Systemic oxygen extraction was increased.	
Ayres et al.[19]	26 and 15	(sufficient time to produce stated COHb (5000 ppm) 8-15 min (1000 ppm)	5-25%	Myocardial and systemic responses	Increased cardiac output and coronary blood flow. Signs suggesting myocardial hypoxia were observed in patients with coronary artery disease.	

TABLE 11-3 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Kandall et al.[129]	15	(none)	1.34-4.92%	Change in COHb with exchange blood transfusions	Elevations in COHb due to receiving transfused blood could not be shown to have any adverse effect on the recipient.	
Middleton et al[139]	22	1.5 hr (20-210 ppm)	(not known)	Carbon monoxide accumulation in closed circle anesthesia systems	Closed system anesthetic techniques allow the accumulation of endogenous and exogenous CO, producing minimal decremental effects.	
Aronow et al.[6]	10	1.5 hr (42-63 ppm)	3.8-8%	Symptoms of angina pectoris	Following exposure to highway air, angina pectoris developed sooner after less work.	
Anderson et al.[2]	10	4 hr (50 and 100 ppm)	mean 2.9% and 4.5%	Onset and duration of angina pectoris	Exposure to low concentrations of CO produced anginal pain of greater duration after less exercise.	
Aronow and Isbell[7]	10	2 hr (50 ppm)	mean 2.68%	Exercise-induced angina pectoris	Exposure to CO produced symptoms of angina sooner and after less cardiac work.	
Kuller et al.[138]	1397	7.7-14 ppm	0.9 to 9.9%	Relationship between exposure and heart attacks	No relationship was established between ambient CO levels and onset of sudden death and myocardial infarction.	This study covers a two-year period and involves deaths due to coronary disease occurring in the Baltimore area.

TABLE 11-3 (continued).

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Hexter and Goldsmith[110]	(not given)	7.3-20.2 ppm	8-17%	Community air pollution and mortality--total number of deaths, day of occurrence, maximum temperature, average CO concentration	A greater number of deaths was shown to have occurred when ambient CO concentrations were higher.	This study covers a period of 4 yrs in Los Angeles County.

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25°C, 760 torr.

The U.S. National Health Survey Examination reported that there were 3,125,000 adults, ages 18 to 79 years, with definite coronary heart disease and another 2,410,000 with suspected heart disease.[240] Many of these individuals, as well as others in the general population, have COHb levels equal to or above 2.5 percent. It would be rash even to suggest that the above-mentioned studies implicate CO as a factor in determining the natural history of heart disease in a community. The necessary epidemiological evidence for an association between frequency of episodes of angina pectoris and community ambient CO levels is lacking; however, it is not presumptuous to state that individuals with cardiac ailments are especially at risk to CO exposures sufficient to produce 2.5 to 3.0 percent COHb.

PULMONARY FUNCTION AND EXERCISE

Maximal exercise can increase the O_2 uptake of the whole body in excess of 20 or more times the resting uptake and will stress the O_2 transport system maximally. Any impairment of O_2 transport, such as could occur when COHb is present, could limit maximal aerobic capacity ($\dot{V}_{O2\ max}$). In fact, it has been appreciated for some time that individuals having a large burden of CO experience difficulty in performing work.

Maximal Work

Roughton and Darling[196] suggested, on theoretical grounds, that work capacity would be reduced to zero when COHb approached 50 percent. Chiodi et al.[41] showed in 1951 that subjects were unable to perform tasks requiring only low levels of physical exertion when their blood COHb reached 40 to 50 percent. Several collapsed while attempting to perform routine laboratory tasks. Chihaia et al.[40] have reported that heavy physical work at low ambient CO levels can induce states of CO poisoning. Goldsmith[82] reported that competitive swimmers have impaired performance when competitive events are conducted in atmospheres containing 34 mg/m^3 (30 ppm) CO originating from traffic.

Oxygen Uptake and Heart Rate

In studies using submaximal exercise for short durations (5 to 60 minutes) it appears that O_2 uptakes during work are unchanged despite the presence of COHb.[35,39,64,65,79,96,168,180,222,223] The only clear indication of physiological load appears to be a slight increase in heart rate. Chevalier et al.[39] and Klein et al.,[132] studying men working at a light work load for a period of five minutes, reported that while the O_2 uptake was not affected when COHb levels were approximately 4 percent (estimated values), there was a significant increase in O_2 debt when this was related to the total O_2 uptake. No one has yet replicated these results on O_2 debt. Five subjects studied by Pirnay et al.[180] performed work for 15 minutes at an O_2 uptake of 1.5 liters per minute. No differences in O_2 uptake were found, even though COHb reached 15 percent. In a rather involved study in which COHb fluctuated between 5 and 17 percent, Klausen et al.[131] found no differences related to CO in energy expenditure when subjects exercised for 15 minutes at 50 percent of their $\dot{V}_{O2\ max}$. Vogel et al.,[223] Vogel and Gleser,[222] and Pirnay et al.[180] reported consistently higher heart rates for selected submaximal work loads, and increased ventilatory volume exchange per unit of O_2 uptake, with COHb levels of 15 to 20 percent.

Gliner et al.[79] studied the responses of two groups of 10 males each (mean age 23.0 and 48.4 years, respectively), one-half of each group being smokers. A work load of 35 percent $\dot{V}_{02\ max}$ was selected (untrained men can work at this level for approximately 8 hours with minimum physiological changes). The subjects worked for 4 hours in an environment containing 57 mg/m^3 (50 ppm) CO. Final COHb levels were 10.3 and 13.2 percent, respectively, for non-smokers and smokers. Ambient temperatures were 25^oC and 35^oC, with a relative humidity of 30 percent. The only significant change was a higher heart rate in the CO environment irrespective of age of subjects, confirming observations previously reported.[180,222,223] Since cardiac index remained constant within individuals at 5-6 liters/(min x m^2) in both filtered air and 57 mg/m^3 (50 ppm) or up to 115 mg/m^3 (100 ppm) CO, stroke output was decreased. The full significance of this change in long-term performance in CO-polluted environments is not apparent at this time.

Despite the wide variability in experimental conditions (duration and magnitude of exercise, level of COHb, methods for giving CO to the subjects) and and the small number and limited age range of subjects exposed, the results from all of the above studies were essentially similar.

Aerobic Capacity

In short-term maximal exercise of several minutes' duration, where capacity for effort is dependent mainly on aerobic metabolism, it is anticipated that maximal aerobic capacity would be diminished approximately in proportion to the level of COHb present in the blood. Such diminution in $\dot{V}_{02\ max}$ when COHb is between 7 and 33 percent has been conclusively observed by a number of investigators.[41,50,64,115,168,180] In the majority of these studies, exercise bouts ranged from 2 to 6 minutes and CO was administered by the breathing either of relatively high concentrations of this gas or of a fixed amount with additional CO to maintain the desired levels of COHb. The smoking habits of subjects were not always characterized.

Seppanen[204] determined the physical work capacity of cigarette smokers (20 cigarettes/day) following either smoking or inhalation of CO. A progressive bicycle test was conducted after a subject had breathed room air (2.8 percent COHb), had smoked (9.1 percent COHb), or had breathed boluses of 1100 ppm CO (9.1 percent COHb). The physical work capacities at heart rates of 130, 150, and 170 beats per minute decreased after both CO inhalation and cigarette smoking. The greatest decrease in calculated maximal work was observed after CO inhalation.

In the above-mentioned studies, the levels of COHb were considerably in excess of those occurring in males exposed to the outdoor air of certain metropolitan areas. The initial studies by Horvath's group[61,189,190] were made on subjects breathing 57 mg/m^3 (50 ppm) CO at either of two thermal ambients, namely 25^oC or 35^oC, with a relative humidity of 20 percent. Investigators used a walking test with progressively increasing grade, requiring some 15 to 24 minutes to complete to measure $\dot{V}_{02\ max}$. The two groups consisted of 20 young (24+ years) and 16 middle-aged (48 + years) subjects, both smokers and non-smokers. The middle-aged subjects demonstrated the anticipated decrease in $\dot{V}_{02\ max}$ associated with advancing age. However, the middle-aged non-smokers had a $\dot{V}_{02\ max}$ some 27 percent greater than that of smokers of the same age. During the duration of the test, COHb levels in non-smokers increased from 0.7 to approximately 2.8 percent, while levels in smokers rose from 2.6 to 3.2 percent to 4.1 to 4.5 percent. Control observations of these subjects while they breathed filtered air indicated that COHb decreased in both smokers and non-smokers. The results from these studies[61,79,189,190] failed to demonstrate any reduction in $\dot{V}_{02\ max}$. The decrement in $\dot{V}_{02\ max}$ that occurred as a consequence of working in the hot environment (35°C) was greater than the changes that occurred from breathing CO.

Other cardiovascular, respiratory, metabolic, and temperature measurements made concurrently with the 0_2 uptake studies also failed to show any decrements associated with the CO exposure. The only significant effect related to CO was a decrease in absolute exercise time. This was consistently observed in the non-smoking subjects but not in the smokers. These observations confirmed those found earlier by Ekblom and Huot[64] who, however, reported a surprisingly large decrease (38 percent) in work time at 7 percent COHb. Aronow and Cassidy[10] found a slight decrease in work time during a maximal exercise test using 10 middle-aged (50.7 years) subjects. Their reported level of 4 percent COHb in subjects who had breathed 115 mg/m^3 (100 ppm) CO for 1 hour is what would be expected with an initial control level of 1.67 percent. One of 10 subjects developed ischemic ST-segment depression after maximal exercise following CO exposure. No electrocardiographic changes were observed in the subjects studied by Horvath's group.[61,79,189,190] Nielsen[168] found that subjects exercising under a CO load developed higher internal body temperatures. Reductions in skin conductance suggested a redistribution of the circulation to the working muscle and away from the skin.

Horvath and coworkers[61,79,189,190] had some concern about the changes in COHb levels in their smokers and non-smokers as well as about the lack of change in $\dot{V}_{02\ max}$ under the ambient and exercise conditions previously employed. They developed a more precise method to regulate relatively low levels of COHb (Figure 11-1).[56] It is of some importance that they found that a low ambient level of CO can be quite effective in maintaining a previously produced high blood COHb concentration. These data suggested that the ambient level of CO may have little to do with the absolute level of COHb present in an individual. In one experiment,[115] a double-blind method was again used in which subjects breathed either filtered air or air with CO that resulted in stable levels of COHb. The data clearly indicated that a threshold level of COHb must be present before significant physiological alterations can be demonstrated. Statistically significant decreases in $\dot{V}_{02\ max}$ were noted when COHb levels exceeded 4.3 percent. Although this was a double-blind, randomized study in which neither the investigators nor the subjects knew the composition of the air breathed, it was subsequently determined that all subjects correctly identified when they had been exposed to the highest level of ambient CO. In all instances they noted a heaviness of the lower extremities and greater difficulty in the task. Ekblom et al.,[58] utilizing a similar technique, raised COHb to 15 percent. The reduction in $\dot{V}_{02\ max}$ was expected. Maximum cardiac output was decreased,

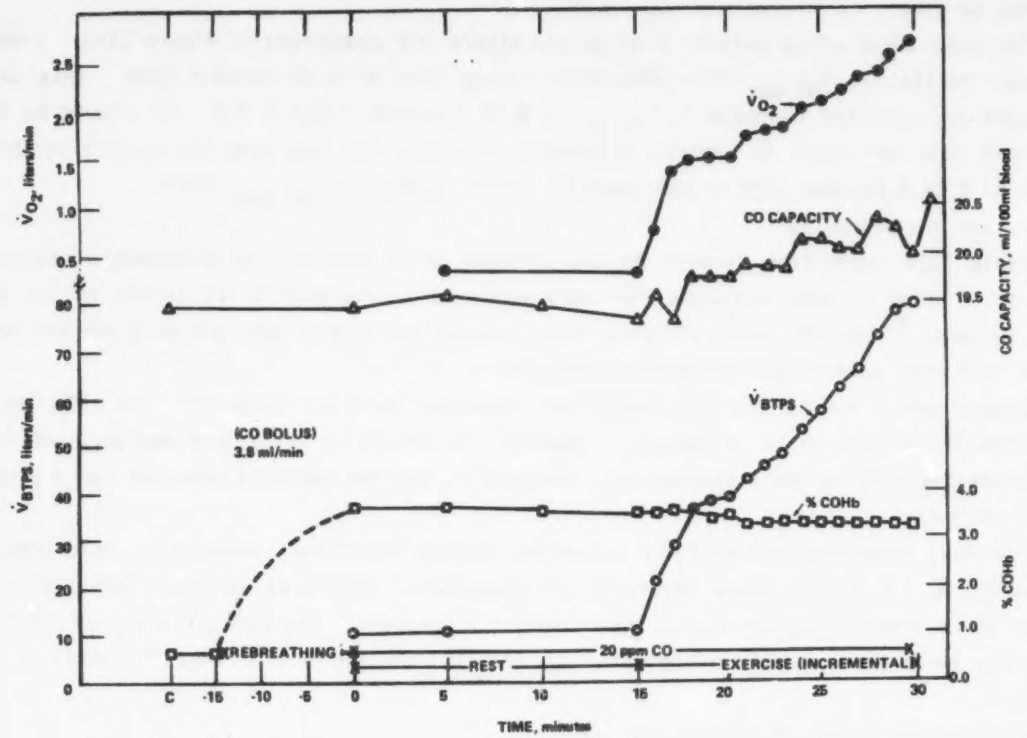

Figure 11-1. The maintenance of requested COHb level in a subject during rest and at various work levels with a widely ranging ventilatory exchange. Control level of COHb was 0.6% prior to the administration of the initial bolus of CO to raise COHb to desired level; a total of 34.2 ml of CO STPD was given. (Used with permission of The American Physiological Society 38:366-368, 1975.)

however, due to decreased stroke volume. Mean myoglobin Po_2 was found by Clark and Coburn[44] to decrease during exercise at $\dot{V}_{02\ max}$. During exhaustive exercise Po_2 increased, suggesting facilitation of O_2 offloading; but when a COHb level of 5 percent was present during exercise, Po_2 decreased. Though the experiment was conducted in Denver (1700 m altitude), subjects having a burden of 5 percent COHb exhibited a decrement in maximum performance similar to that observed by others in subjects at sea level.

The data obtained by Horvath's group and others are summarized in Figure 11-2. There is a linear decline in $\dot{V}_{02\ max}$ when COHb levels range from 4 to 33 percent COHb. This can be expressed as: percent decrease in $\dot{V}_{02\ max}$ = 0.91 (percent COHb) + 2.2. It should be noted that this does not apply to smokers in Horvath's series, who had COHb levels considerably in excess of 4 to 5 percent with no decrement in their respective $\dot{V}_{02\ max}$ values.

Conclusions and Discussion

Table 11-4 summarizes studies on the effects of CO exposure on pulmonary function and exercise. There is some evidence that work capacity is affected at CO levels as low as 34 mg/m^3 (30 ppm),[51] but the study yielding those results was poorly controlled, since ambient CO levels were used rather than systematic exposures.

Oxygen uptake during short exposures and submaximal work are apparently not affected even when COHb levels are 15 to 20 percent. However, it should be noted that healthy individuals were generally used in these studies and, frequently, too few subjects were run for a study to be definitive.

The most carefully executed and extensive studies are those involving aerobic capacity. Obviously, CO can modify these physiological responses. The level of blood COHb required to induce these effects appears to be approximately 5 percent. The concentration of CO in the blood may be a more sensitive indicator of effect than the simple ambient levels of this pollutant.

INTERACTIONS WITH OTHER POLLUTANTS AND DRUGS

Other Air Pollutants

There are many other compounds in polluted atmospheres that have been demonstrated to have deleterious effects on physiological functions. Horvath and his group[61,79,189,190] have shown that combinations of 57 mg/m^3 (50 ppm) CO and 1.33 mg/m^3 (0.21 ppm) peroxyacetylnitrate (PAN) exerted no greater effect on the work capacity of healthy men (young and middle-aged, smokers and non-smokers) than that of CO alone. However, it appeared that slightly greater concentrations of either component could have led to significant differences in response. Hackney et al.[99,100] found no consistent changes (synergistic or additive) in pulmonary functions in a 2-hour exposure of young male subjects to a combination of three pollutants: SO_2, O_3, and CO (34 mg/m^3, 30 ppm). It has been reported by Mamatashvili,[151] who exposed human volunteers to low concentrations of CO and SO_2, that each component produced independent deleterious effects on light and color sensitivity. An 8-hour exposure to mean ambient concentrations of CO and ammonia resulted in insignificant physiological and biochemical

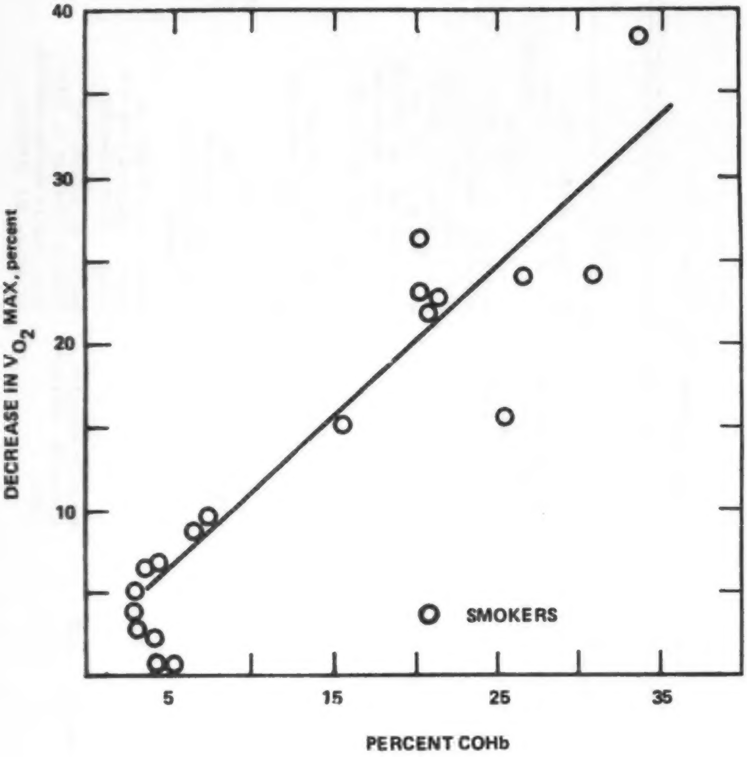

Figure 11-2. Relationship between COHb and decrement in maximum aerobic power.

TABLE 11-4. SUMMARY OF DATA ON EFFECTS OF CO ON HUMAN PULMONARY FUNCTION AND EXERCISE

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Chiodi et al.[41]	dogs n = 2 men n = 4	>70 min (0.15-0.35%)	16-52%	Pulmonary ventilation, cardiac output, plasma pH and respiratory center response to high CO_2	No hyperpnea observable during rest with acute and severe CO poisoning. Arterial P_{CO_2} increased and pH became acidic. In severe poisoning, respiratory center depressed. Cardiac output increased slightly with COHb up to 30%; increased as much as 50% with COHb up to 50%. Depressive action on the respiratory center.	
Chihaia et al.[40]	5	Job exposure	up to 50%	Physical work	Unable to perform low-oxidation level work after 40 to 50% COHb.	
Goldsmith[82]	(not given)	Up to 2 hr (11-30 ppm)	(not given)	Performance of competitive swimmers	COHb levels compared with inhaled cigarette smoke and affected performance of swimmers.	COHb was established by measuring expired-air CO samples.
Chevalier et al.[39]	10	2.5-3.5 min (0.5%)	3.95%	Oxygen uptake	Greater oxygen debt per greater oxygen uptake when compared with nonsmokers.	
Pirnay et al.[180]	5	(not stated)	15%	Muscular exercise during CO intoxication	Maximal O_2 consumption lowered. Greater ventilation induced during exercise. O_2 uptake not affected.	

TABLE 11-4 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Ekblom and Huot[64]	10	15 min (in quantity theoretically determined to obtain stated blood values)	7 and 20%	Response to maximal and submaximal work load at different COHb levels	Maximal physical performance was reduced with increasing levels of COHb, as was V_{O2max}. Highest heart rate decreased at 20% COHb during maximal work and increased during submaximal work at both 7% and 20% levels. There was a more significant change in O_2 deficit at 20% COHb than at 7% COHb.	
Horvath et al.[115]	4	Build-up and maintenance dose (75 and 100 ppm) for a period 15 min + exercise time		2.7, 4.5 and 5.2%	Maximal aerobic capacity at different levels of COHb	$V_{O2\ max}$ lower for COHb levels of 4% or greater. Ventilatory volumes were significantly lower with COHb 3.2-3.4%.
Neilsen[168]	(not given)	(not given)	(not given)	Thermoregulation and work	Equilibrium body temperature was higher. Acute exposure to altitude left temperature level unchanged.	
Pirnay et al.[180]	5	(not stated)	15%	Muscular exercise during CO intoxication	Maximal O_2 consumption was lowered. Greater ventilation was induced during exercise. O_2 uptake not affected.	
Drinkwater et al.[61]	20	~20 min, depending on subject; 50 ppm		3.17%	Exercise and heat stress	Exposure effectively reduced work time of nonsmokers and elicited changes in respiratory patterns of both smokers and nonsmokers.

TABLE 11-4 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Raven et al.[190]	16	50 ppm	2.31-5.54%	Body temperature, cardiorespiratory and metabolic responses	Total working time reduced with exposure to CO at lower (25°C) temperature. Older nonsmokers had decrement in V_{O2} max.	
Aronow and Cassidy[10]	10	1 hr 100 ppm	3.95%	Maximal treadmill exercise	Mean exercise time significantly reduced.	
Raven et al.[189]	16	(no exposure time given) 50 ppm	Increased (14% for smokers) 200% for for non-smokers	Body temperature, cardiorespiratory and metabolic responses during tests of maximal aerobic power under 2 temperature conditions (25° and 35°C)	No significant change in maximum aerobic power. Total working time decreased at 25°C ambient temperature. Older nonsmokers showed decrement in V_{O2} max. Older smokers showed no change. Regardless of ambient conditions, smokers had significantly lower aerobic power than nonsmokers. Aerobic power of older smokers 26% lower than that of younger smokers.	
Ekblom et al.[65]	9	15 min (repeated once) levels to produce stated COHb	12.8-15.8%	Changes in arterial O_2 content in relation to circulation and physical performance	Maximal physical performance decreased after CO exposure. Lower cardiac output during CO-induced hypoxia. Maximum heart rate was significantly lower in 1 subject at levels >13%.	
Clark and Coburn[44]	21	(not given)	(not given)	Mean myoglobin oxygen tension during exercise at maximal oxygen uptake	CO shifted out of the vascular compartment; implied that the CO taken up by muscle tissue containing myoglobin.	

TABLE 11-4 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Klausen et al.[231]	8	(not given)	(not given)	Circulation, metabolism, ventilation	No change in ventilation at rest, but changes present in work.	
Vogel et al.[223]	16	1 hr 225 ppm	17-18%	Physical work capacity	No impairment in ability to do heavy work.	
Vogel and Gleser[222]	8	225 ppm	18-20%	Effect on O_2 transport during exercise, compared with hypobaric hypoxia	No significant differences in O_2 transport though with CO hypoxia a lack of cardiovascular response at rest and a lesser ventilation with exercise was apparent.	
Gliner et al.[79]	19	4 hr 50 ppm	4.6 to 6.8%	Physiologic response to long-term work and thermal stress	Decrement of stroke volume which increased with higher ambient temperature. Heart rate was increased in CO.	
Collier et al.[50]	9	Loading dose: 10,000 ppm to produce mean COHb of 8.9%; maintenance dose: 60-70 ppm for 5 mins (to produce mean of 7.8%).	8.9% and 7.8%	Physiological adaptations and exercise in normal healthy males	Minute volume + breathing frequency increased only during exercise, O_2 consumption and arteriovenous O_2 content difference during exercise. Venous O_2 content and venous Po_2 decreased with exercise and at rest.	

TABLE 11-4 (continued)

Reference	No. of subjects	Exposure[a]	COHb	Dependent variable	Results	Comment
Klein et al.[132]	4	(not given)	4-12%	Hemoglobin affinity for oxygen in relation to exercise and chronic elevation of COHb	Facilitated O_2 off-loading, but the mechanisms and significance remain to be established. Does not induce compensatory changes in P_{50} to facilitate tissue oxygenation during moderate elevation of COHb .	

[a] Conversion of CO in ppm to mg/m^3: ppm x 1.15 = mg/m^3 at 25°C and 760 torr.

effects on young healthy non-smokers.[219] An additive effect was observed by Elfinova et al.[66] for a combination, at low concentrations, of CO, phenol, and dust.

Gzegocskij[97] reported that the presence of CO and nitrogen oxides in dust-laden air could reinforce the toxic effect of silicon dioxide and hasten the development of silicosis.

Other Environmental Parameters

The organism's response to the presence of CO may well be modified by the presence of other environmental factors such as ambient temperature, relative humidity, and barometric pressure. Korenevskaja[134] indicated that high ambient temperatures reinforce the toxic effect of CO and that the presence of CO lowers the body's resistance to overheating. Men working for 4 hours in an ambient temperature of 35°C and 20 percent relative humidity and exposed to a CO concentration of 57 mg/m^3 (50 ppm) failed to show synergistic effects.[61,79] Horvath's group[190] reported reduced working time with CO at 25°C, but not at 35°C. Experimental animal studies have shown the importance of temperature effects on survival at high CO exposure levels.

Alcohol

Rockwell and Weir[194] evaluated the interactive effects of CO and alcohol on highway driving performance in four young, non-smoking college students. Carboxyhemoglobin levels were 0, 2, 8 and 12 percent, and blood alcohol was 0.05 percent. Perceptual narrowing and decreased eye movement were noted under increasing COHb levels, but there was an alcohol-CO synergistic interaction only in curve negotiation tasks at the 12 percent COHb level.

Stewart's group[157] has recently evaluated behavioral functions in relation to the hypothesis that alcohol ingestion (59 mg percent blood level) would potentiate any deleterious CO effects. Neither the presence of COHb levels of 8.8 percent nor the blood alcohol level produced deleterious performances.

Smoking

A common source of CO for the general population comes from tobacco smoking, with other primary sources arising from the environment. Exposure to smoking primarily affects the COHb level of the smoker himself,[128,141,198] but in some circumstances, such as poorly ventilated spaces, smokers provide a source that may affect other occupants. In addition to CO, other products inhaled by the smoker may produce subtle physiological and biochemical effects on both the smoker and those individuals breathing either the pre-inhaled materials or the smoker's exhaled products.[198,209] Possible pathological changes due to the interaction of CO and other constituents of smoke that may occur in the lungs and other tissues remain to be elucidated.

Those interested in the problems related to smoking tobacco, i.e., carcinogenesis, and cardiovascular and pulmonary disease, should refer to documents specifically concerned with these matters.[70,105,182] Prospective and retrospective epidemiological studies have identified cigarette smoking as one of the major factors in the development of coronary heart disease (CHD). The risk of developing CHD for pipe and cigar smokers is apparently much less than it is for cigarette smokers but more than for non-smokers. Tobacco smoking may contribute to the development and aggravation of CHD through the action of several independent or complementary mechanisms, one of which is the formation of significant levels of COHb.[184]

In the report of their epidemiological study in Baltimore, Kuller et al.[138] have stated that if there is an association between CO and heart attacks, the significant exposures are probably related to microenvironmental factors and cigarette smoking rather than community air pollution. They did note, however, that relatively few heart attacks occur while an individual is smoking a cigarette. Astrup[15] has suggested that intermittent exposure to CO may be regarded as putting smokers at a much higher risk than non-smokers for the development of arterial diseases. Wald et al.[226] and Ball and Turner[21] have come to similar conclusions.

Smoking of cigarettes has been found to result in higher COHb levels than exposure to street air levels of CO.[38,198] Smokers who were manual workers had lower COHb levels than smokers who were sedentary workers, probably because of the increased ventilation required in the occupations of the manual workers.[38,200] Srch[209] performed tests on two smokers and two nonsmokers in a small car. Before entering the car, the smokers and non-smokers had COHb levels of 5 and 2 percent, respectively. Each smoker smoked five cigarettes with the windows and doors closed. At the end of the 60-minute test, the respective COHb in the smokers and non-smokers had increased to 10 and 5 percent. Other studies have reported essentially similar patterns of accumulation in non-smoking individuals exposed to smokers in closed spaces. The pattern of accumulating CO (as well as other products) in closed spaces has been described,[55,121,229] and a mathematical model for calculating the build-up of CO and the resultant COHb levels has been developed.[127]

The quantity of CO actually entering the lung depends upon the form in which tobacco is smoked, the pattern of smoking, and the depth of inhalation.[192] Very little CO is absorbed in the mouth and larynx (approximately 5 percent), so that most of the CO available for transfer to Hb must reach the alveoli in order to raise the level of COHb present in the blood stream. Cigarette smokers inhale more than cigar smokers, and the latter less than pipe smokers; but individual differences in this pattern are quite marked. Heavy cigarette smokers have COHb levels as high as 15 to 17 percent. The CO concentration in cigarette smoke is approximately 4.5 percent.[70,106,107,227] It has been estimated that a cigarette smoker may be exposed to 458 to 572 mg/m^3 (400 to 500 ppm) CO for the approximately six minutes it takes to smoke a cigarette. Landaw[141] noted that a smoker's COHb level increased 1 to 9 percent during periods of active smoking. He also presented data suggesting that the half-time of CO elimination in smokers was approximately 291 minutes. Smith and Landaw[206,207] reported that smokers (mean COHb of 11.6 percent) had increased red-cell volumes or reduced plasma volumes, or both. Pankow et al.[239] have raised the question as to whether or not these changes represent an adaptive response. Figure 11-3 illustrates the pattern of change in COHb in a typical heavy cigarette smoker.[116] An indwelling venous catheter permitted the frequent sampling of this smoker's blood. The subject smoked only during his working hours. When he began to smoke the

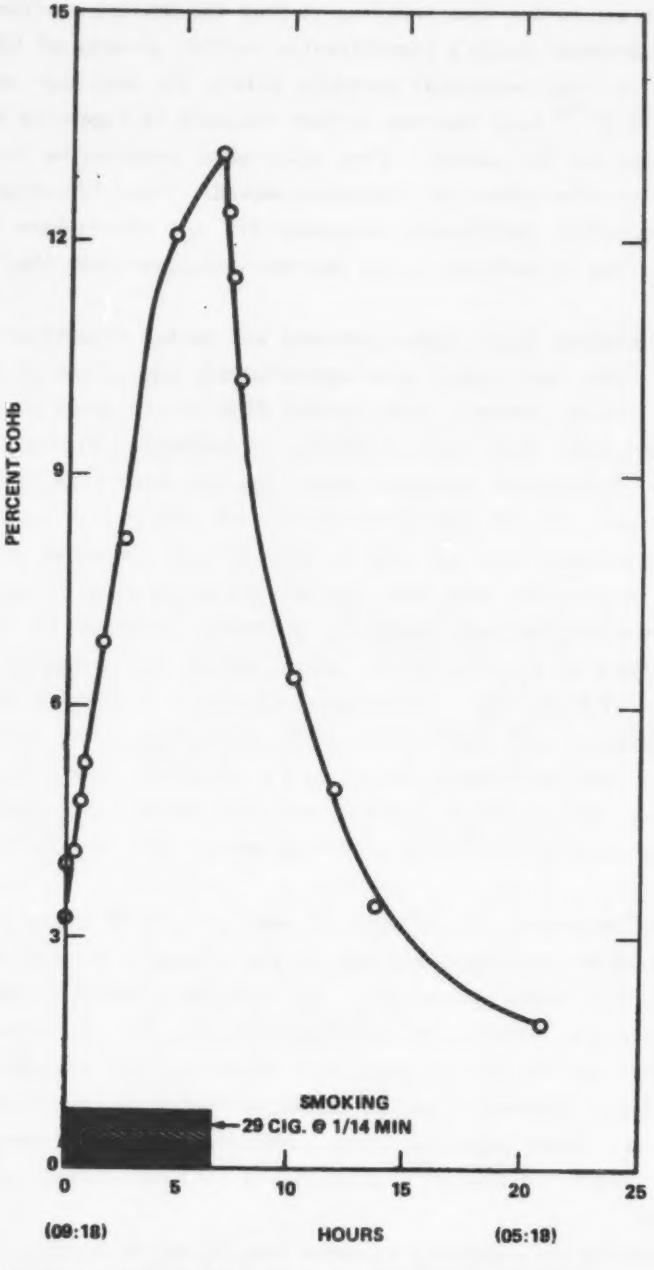

Figure 11-3. Pattern of change in COHb in a typical cigarette

next day, he still had a body burden of 1.7 percent COHb. Cigarette smokers generally are excreting CO into the air rather than inhaling it from the ambient environment.

Low-toxicity cigarettes produce significantly smaller amounts of CO.[49,86,221] However, the smoking pattern of the individual markedly alters the absolute amount of CO inhaled.

Frankenhaeuser et al.[76] have reported another response to cigarette smoking that may have important consequences to the smoker. They observed a progressive increase in adrenaline (epinephrine) excretion with number of cigarettes smoked. These investigators have also found that certain psychophysical performance measures did not deteriorate if moderate smokers smoked during the testing in contrast to the decrement observed when they did not smoke during testing.[164]

Aronow et al.[9] studied eight angina patients who smoked cigarettes or were given CO to breathe so that the final COHb levels were approximately equivalent (3.90 and 3.86 percent). These patients were already smokers, with initial COHb levels above 2 percent. Catheterization of both left and right ventricles permitted an evaluation of the functions of the myocardium. The major differences observed under the two conditions were as follows: (1) cardiac output decreased with CO inhalation and did not change with smoking; (2) systolic and diastolic arterial pressures did not change with CO but increased with smoking; (3) left ventricular change in pressure with time (dp/dt) decreased with CO but did not change with smoking; (4) left ventricular end diastolic pressure increased in both situations; and, (5) the partial pressure of O_2 in arterial, mixed venous, and coronary sinus blood decreased with CO exposure and with smoking. Furthermore, CO causes a negative inotropic effect on the myocardium that decreases left ventricular dp/dt, decreases stroke index, decreases cardiac index, and increases left ventricular end diastolic pressure. These divergent effects should be further evaluated. Aronow et al.[4] stated that the increased systemic blood pressure and heart rates that are observed following cigarette smoking were related to the nicotine in the cigarette.

A critical problem arises in attempts to separate the CO effects of cigarette smoking from the effects of other substances present in the inhaled cigarette smoke. Aronow et al.[5] had male angina patients smoke lettuce leaf, non-nicotine cigarettes, which resulted in blood COHb levels of 7.8 percent. Heart rate and blood pressure were unaffected by this smoking but again angina occurred earlier during exertion. These data may suggest that the presence of COHb following smoking of cigarettes may be the major factor in the development of angina pectoris during exercise. Chest pain and electrocardiographic changes have been associated with acute CO poisoning. Wald and Howard[227] have stated in their overall review on smoking, CO, and arterial disease:

> "There is at present only indirect evidence that CO may be a cause of atheroma in man and for the present, however, it is necessary to reserve judgment on whether CO is a cause of arterial disease, while at the same time suspecting that it may be the principal agent in tobacco smoke."

Aronow[7] and coworkers, as well as Anderson et al.,[2] have shown that in patients with ischemic heart disease, exercise-induced angina occurs earlier when the patients are exposed to low levels of CO. Carbon monoxide exposure also exacerbates and prolongs the pain of intermittent claudication in patients with this disease.[8] The potential deleterious influence of cigarette smoking and/or CO exposure on the pregnant woman, fetus, and neonate is considered later in this chapter. The only direct evidence that CO adversely influences fetal development was derived from studies conducted on rabbits[17] and rats.[68,69]

A number of studies have suggested that cigarette smoking reduces work capacity[80,119,135,182] in direct relation to the level of COHb present in the working subject. In young smokers (21 to 30 years of age) no differences in maximal aerobic power were observed despite reductions in vital capacity and maximum breathing capacities.[189] Older smokers (40 to 57 years of age) had significantly lower (27 percent) aerobic power than comparably aged non-smokers.[190] Younger smokers had only a 6 percent lower aerobic power than nonsmokers of similar age. McHenry et al.[156] found that the duration of maximal exercise and maximal heart rate was significantly shorter in smokers and former smokers than in nonsmokers. Maximal systolic blood pressure during exercise was greater in smokers. Tobacco smoking decreased $\dot{V}_{O2\ max}$ even in young moderate smokers.[111] The effect of passive smoking (i.e., exposure to three individuals smoking five cigarettes each) on non-smoking persons with exercise-induced angina has been reported.[12] Their exercise time to the onset of angina was decreased 22 and 38 percent, respectively, from exposure in a well ventilated and an unventilated room. Corresponding blood COHb levels were 1.77 and 2.28 percent in these subjects. There still remains some question as to the role of other materials in cigarette smoke in producing this reduced performance.

Smokers may have early closure of small airways, especially when supine.[108] The diffusing capacity for CO in young smokers as well as older smokers is impaired.[108,239] Other physiological changes have also been reported.[31] The potential hazard of rapid smoking utilized in the stimulus-satiation method to help smokers break the smoking habit has been identified by Miller et al.[160] Carboxyhemoglobin levels above 22 percent can occur.

Conclusions and Discussion

While it is important from the point of view of general and theoretical information to know how CO alone affects various physiological and behavioral systems, CO does not occur by itself in the actual environment. The data relating CO to other pollutants is so sparse, however, that almost no pattern can be discerned. Both human and laboratory animal studies suggest cases in which CO either additively or synergistically combines with other airborne pollutants to produce increased effects; but there is usually only one study per pollutant combination, and even those do not give parametric data from which dose-response curves or thresholds might be estimated. There is a definite need for systematically obtained information about real-life combinations of other pollutants with CO.

In both human and experimental animal studies, the data regarding alcohol in combination with CO are only suggestive. This frequently occurring combination is of such import as to urgently require further research, especially with regard to behavior and psychomotor performance. Other drugs (both therapeutic and illicit) that would be expected to interact with CO have not been studied. It would seem to be of paramount importance to know the combined effect of CO and such drugs as tranquilizers, sedatives, and illicit psychotropic drugs. Data from experimental animal studies strongly indicate that the effects of such drugs are potentiated and/or altered by CO exposure. The possibility that CO may potentiate or counteract the effects of drugs designed to alleviate cardiovascular or pulmonary conditions is quite important in view of COHb levels attributable to environmental sources and smoking.

Smoking is another source of CO to the smoker and others, as well as a source of other chemicals with which environmental CO levels could interact. Available data strongly suggest that chronic CO exposure through smoking produces cardiopulmonary damage, but the interaction with other products of smoking confounds the results. Data on the effects of environmental CO increments in addition to COHb built up due to smoking have produced results which in some cases imply additive effects and in other instances imply adaptation to COHb. There is need for further systematic and parametric research to describe these relationships.

HIGH ALTITUDES - MECHANISMS

Precise data on the potential scope of the problems attributable to CO for high altitude residents and visitors are not available. Approximately 2.2 million people live at altitudes land elevations above 1524 meters in the United States. These figures do not present a complete picture of potential numbers of individuals who may be subjected to CO at these altitudes because the tourist population in these areas is high in both summer and winter. Furthermore, proper tuning of automobiles for high altitude traveling is uncommon, and the influx of visitors and cars with their greater emissions of CO and other contaminants may prove to be an important factor in raising pollution exposure to an unacceptable point. At 1540 meters, each cubic meter of air contains approximately 18 percent less oxygen than at sea level. Therefore, air concentrations of carbon monoxide in a city like Denver will be 22 percent higher than at sea level (e.g., a 10 mg/m^3, 8-hour average is equivalent to 11.8 mg/m^3 at Denver's altitude).

Physiological Results

Carbon monoxide exposure may aggravate the O_2 deficiency present at high altitudes. When high altitude and CO exposures are combined (Table 11-5), the effects on O_2 availability in blood are apparently additive. It should be noted, however, that decreased O_2 in the air and increased COHb produce different physiologic responses. They have different effects on blood Po_2, on the affinity of O_2 for Hb, on the extent of O_2Hb saturation (CO hypoxemia shifts the O_2Hb dissociation curve to the left, and a decrease in arterial Po_2 shifts it to the right), and on ventilatory drive.

TABLE 11-5. APPROXIMATE PHYSIOLOGICALLY EQUIVALENT ALTITUDES AT EQUILIBRIUM WITH AMBIENT CO LEVELS

Ambient CO concentration		Actual Altitude (meters)		
mg/m^3	ppm	0 (sea level)	1524	3048
0	0	0	1524	3048
28.6	25	1829	2530	3962
57.3	50	3048	3658	4694
114.5	100	3749	4663	5486

Forbes et al.[75] reported that during light activity at an altitude of 4875 meters, CO uptake was increased, probably because of the hyperventilation at that altitude caused by the respiratory stimulus of decreased Po_2. Evidence that CO elimination was similar at sea level and at altitudes up to 10,000 meters has been obtained by different investigators.[87,203] Increased ambient temperatures up to 35°C and hard physical work increased the rate of elimination.[225] Pitts and Pace[181] stated that every 1 percent increase in COHb (up to 13 percent) was equivalent to a 109-meter rise in altitude, if the subjects were at altitudes of 2100 to 3070 meters. Their observations were based on changes in the heart rate response to work. Subjects who may have been smokers were not identified.

Two groups of investigators have presented data comparing the physiological responses of subjects to altitude and CO where the hypoxemia due to altitude and the presence of COHb were approximately equivalent. In one study[14] the COHb level varied around 12 percent (although the mode of presentation of CO was such that COHb ranged during the CO exposures from 5 to 20 percent) and the altitude comparison was conducted at 3977 meters. The second study[203] compared responses of subjects at altitudes of 4000 meters and a COHb content of 20 percent. In both studies, COHb content was in excess of that anticipated for typical ambient pollution. However, it was suggested that the effects attributable to CO and to altitude were equivalent. Wagner et al.[225] studied smokers and nonsmokers who exercised at 53 percent of their $\dot{V}_{O2\ max}$ and at 760 and 523 torr. Carboxyhemoglobin levels were raised to 4.2 percent. While at altitude and in an altitude chamber with elevated COHb levels, nonsmokers increased their cardiac output and decreased their arterial-mixed venous O_2 difference. Smokers did not respond in similar manner. Smokers may have developed some degree of adaptation to CO.

Parving[178] exposed humans to CO to produce 20 percent COHb and to a simulated high altitude sufficient to produce an equivalent arterial blood oxygen saturation. Exposure times were 3 to 5 hours. The results showed increased capillary permeability for proteins during exposure to CO but not during exposure to simulated high altitude. It was also shown that plasma volume decreased significantly during the simulated high altitude exposure but not during CO exposure. The plasma volume was explained as due to hypoxia-induced hyperventilation, but the effect on capillary wall permeability appears to be unique to CO and therefore apparently represents a non-hypoxic short-term effect.

On theoretical grounds it has been recommended that the ambient CO in tunnels being constructed at 3859 meters should not exceed 29 mg/m^3 (25 ppm).[162] The maximal aerobic capacity is reduced approximately 20 percent in individuals at an altitude of 3085 meters. Weiser et al.[232] reported that max $\dot{V}_{O2}$ was significantly impaired in subjects living at 1700 meters when their COHb levels were 5 percent. However, this decrement is similar to that seen in sea level residents. No data are available for higher altitudes. Brewer et al.[33] conducted a study on residents of Leadville, Colorado (3085 meters). The mean COHb level in smokers at that altitude was higher than that of smokers at sea level. This increased degree of hypoxemia may have contributed to an elevated red cell mass, since individuals who stopped smoking demonstrated a reduction in their red cell mass. Kurt et al.[139,140] demonstrated that ambient CO levels in Denver, Colorado had a significant, low-level association with the number of patients reporting to an emergency room with acute cardiorespiratory complaints.

Behavioral and Central Nervous System

The most supportive information on the additive nature of CO hypoxia and hypoxic hypoxia originates from psychophysiologic studies, and even these are not as conclusive as one would desire. Blackmore[28] analyzed the cause of aircraft accidents in Britain, finding that COHb levels provided valuable information relative to altitude and CO sources. The relatively high levels found could be attributed to equipment failure, smoking, and fires. No data are available on the effects of CO on native inhabitants of high altitudes or on the reactions of these natives when they are suddenly removed to sea level and possible high ambient CO concentrations.

McFarland et al.[104,153] showed that changes in visual threshold occurred at a simulated altitude of approximately 2425 meters. Vollmer et al.[224] studied the effects of CO at simulated altitudes of 3070 and 4555 meters and reported that there were no additive effects of CO and altitude. They suggested that the effects of CO were masked by some compensatory mechanisms. The data presented were not convincing. Lilienthal and Fugitt[144] indicated that a combination of altitude (1540 meters) and 5 to 9 percent COHb induced a decrease in flicker fusion frequency, although either one alone had no effect. They also reported that the presence of 8 to 10 percent COHb was effective in reducing altitude tolerance by some 1215 meters.

Conclusions and Discussion of Carbon Monoxide and High Altitude Combinations

Data from both physiological and behavioral studies on humans seem to indicate a simple additive effect of CO and high altitudes. They both reduce O_2 availability, and there are data that allow estimation of their common effect on O_2 levels.

It would be erroneous to infer that CO hypoxia and hypoxic hypoxia are equivalent states or produce equivalent results. They appear to do so at equilibrium states, but CO uptake and elimination produce a slower rate of O_2 change than hypoxic hypoxia. Hypoxic hypoxia also produces hyperventilation; CO hypoxia does not.

Data from experimental animal studies imply that for some physiological functions, CO has additional non-hypoxic effects that might act to impair functioning of some systems. Although such additional impairment might represent unanticipated, more-than-additive effects of CO and high altitude, data from human studies on this are lacking.

ADAPTATION, HABITUATION, AND COMPENSATORY MECHANISMS

Extensive discussion of these topics was given in Chapter 10. There the term "adaptation" was used to refer to long-term effects, and the term "habituation" was used to refer to short term effects. This convention will be continued here.

In the previous chapter, experimental animal data were reviewed showing that COHb levels produced physiological responses that tended to offset other deleterious effects of CO. Such responses were: (1) increased coronary blood flow, (2) increased cerebral blood flow, (3) increased hemoglobin through increased hemopoeisis, and (4) increased O_2 consumption in muscle. Where possible, an evaluation of the completeness of such so-called compensatory responses was made, and in general the compensation appeared to be only partial. There was also some evidence that such compensation on a long-term basis might have undesirable side effects.

Adaptation and Other Long-Term Effects

The presence of a clinical state of chronic CO poisoning, with the implication that adaptation to CO occurs in humans, has not been verified. If it existed, such a state should have been identified by studies on long-term heavy smokers or on individuals exposed to environmental sources of CO. Early concern in England and Scandinavia with CO intoxication led to studies suggesting the possibility of such a condition.[94,130] However, problems regarding the employment of high levels of inspired CO (several hundred parts per million) and inadequate experimental methods have resulted in some skepticism of the conclusions presented. Killick,[130] using herself as a subject, reported that she developed acclimatization as evidenced by diminished symptoms, slower heart rate, and the attainment of a lower COHb equilibrium level following exposure to a given inspired CO concentration. Interestingly, Haldane and Priestly[103] had earlier reported a similar finding as to the attainment of a different COHb equilibrium following exposure to a fixed level of CO in the ambient air. Additional information on other possible adaptation effects in the pre-1940 literature can be found in Killick's review.[130]

The mechanism by which long-term adaptation would occur, if it could be demonstrated in human beings, is assumed to be an increased Hb concentration via a several-day increase in hemopoeisis. If, in fact, such data from human studies were available, the question of the completeness of the adaptation would be very important, as would the question of the undesirable chronic side effects of the compensation. If an appreciable amount of compensation occurs in man, then it could be inferred that CO effects might be much more extreme in subjects with impaired compensatory mechanisms.

Habituation and Short-Term Effects

The only evidence for short-term COHb compensation in man is indirect. From experimental animal studies it is known that coronary blood flow is increased with COHb, and from human studies it is known that subjects with impaired cardiac functioning have the lowest threshold to CO-induced decrements. The implication is that in some cases of cardiac impairment, the short-term compensatory mechanism is impaired and thus the threshold is lowered.

In a few instances of behavioral testing, it has appeared that decrements due to CO have occurred only at very low levels or at early exposure times and have, in the same studies, not appeared at higher or longer exposures. This has led to the hypothesis that there might be some threshold or time lag in a compensatory mechanism such as increased cerebral blood flow (CBF). Not only is there no direct physiological evidence from human or experimental animal studies for such a threshold or time lag, but it would appear to be more conservative to assume that the observed behavioral effects were due to possible non-random sampling.

The idea of a threshold or a time lag in compensatory mechanisms should not be rejected. There simply is no direct evidence. Studies should be performed which (1) measure CBF and tissue Po_2 with low COHb levels at various saturation rates to determine early and low level effects accurately and (2) design behavioral studies where threshold effects or time lags are factors in the experimental design that can be explicitly studied.

SPECIAL GROUPS AT RISK

As discussed in Chapter 10, it is known from both theoretical work and experimental animal research that certain groups in the population are at a higher than normal risk of detrimental effects from CO exposure. The list of such groups from Chapter 10 included the fetus, subjects with health impairments, subjects who are under the influence of drugs, and subjects who have not been adapted to high altitude and are then exposed to a combination of high altitude and CO. Even in laboratory animals, there is too little information about CO effects in these special risk groups to assess the extent of increased risk and the circumstances under which it might occur. In this section, human studies will be reviewed in an attempt to deduce the extent of the problem that has been described in experimental animals.

Fetus

It has been shown in experimental animals that short-term maternal CO exposure results in lower COHb levels in the fetus than in the mother, but has greater detrimental effects on the fetus than on the mother. Long-term maternal CO exposure has been shown to lead to higher fetal than maternal COHb. Fetal uptake and elimination of CO has been shown to be slower than maternal. These data are reviewed in Chapter 10.

Pregnant mothers and their fetuses may be exposed acutely or chronically to CO either by maternal smoking or by environmental pollution. The biologic effects of CO exposure on fetal tissues during intrauterine development or during the newborn period require clarification.

Of the several mechanisms that may account for the influence of CO on developing tissue, the most important is the interference with tissue oxygenation. Carbon monoxide decreases the capacity of Hb to transport 0_2 and shifts the 0_2 saturation curve to the left. The normal arterial Po_2 supplying fetal tissue is approximately 28 torr. This additional shift to the left will tend to decrease further the 0_2 gradient from maternal to fetal blood across the placental tissue. The decreased Po_2 and the diminished 0_2 transport due to the presence of COHb may also produce undesired influences on the fetus.

One of the possible mechanisms by which CO or other components of tobacco smoke may adversely influence fetal development is through interference with the metabolic function of placental cells. These cells have a role in hormone metabolism, as well as in the transport of vitamins, carbohydrates, amino acids, and other substances, through their energy-dependent processes. Tanaka[218] reported that the 0_2 uptake of placenta tissue slices from smoking mothers varied inversely with maternal carboxyhemoglobin (CO_mHb), being markedly reduced when CO_mHb was greater than 7.0 percent. The preponderance of evidence concerning CO_mHb levels, along with fetal and perinatal exposure, tends to warrant the minimization of exogenous CO sources to which this group might be exposed. Longo[148] has reviewed the pertinent literature up to 1977, and Hill et al.[112] have provided a mathematical model for the exchange of CO between the fetus and the mother.

Another factor that may produce differential effects on the fetus is related to the endogenous production of CO by pregnant women. Longo[147] indicates that non-smoking pregnant women produce 0.9 ml CO/hr, and non-pregnant women produce 0.39 ml CO/hr.[149] Fetal endogenous CO production accounts for 3 percent of the total COHb present in the blood of a non-smoking normal pregnant woman. The source of the remainder is unknown, although it may be partly accounted for by the increased red cell mass of the pregnant woman. Even though the hyperventilation of pregnancy may partially compensate for the increased CO production in the absence of exogenous exposure, the CO_mHb still remains at about 13 percent above that in non-pregnant women.[147] It should be noted that post-partum (24-hours) females may be producing three times as much CO as a near-term non-smoking pregnant woman. Hemolytic disease of newborn infants (physiological jaundice) produces a high level COHb resulting from endogenous production and so provides a further stress to the infant.[167,175]

Smoking mothers have been reported to have from 2 to 14 percent COHb, while COHb levels in the fetuses ranged from 2.4 to 9.8 percent. These values may not represent conditions present during pregnancy, since these data were obtained just prior to birth. The newborn are also subject to ambient levels of CO. Berhman et al.[24] measured COHb in 16 relatively normal newborns in a downtown Chicago nursery. Carboxyhemoglobin was found to be as high as 6.98 percent. These investigators indicated that the absolute COHb levels were related to ambient levels of CO. This conclusion is somewhat doubtful since the monitoring reference site was some 1.5 miles from the nursery. The investigators reported no untoward clinical effects from these levels of COHb. However, the high levels of COHb in neonates are of some concern and warrant further investigation.

Several studies[16,150] have demonstrated that babies delivered of mothers who smoke cigarettes weigh less than those delivered of nonsmoking mothers. Relative maternal, fetal, or placental hypoxia may be responsible, as suggested by the observation that infants born at higher altitudes also weigh less than those born at sea level.[143]

Maternal smoking probably constitutes the most frequent source of fetal exposure to CO. There is some question as to the relationship of fetal deaths to maternal smoking but there is no doubt that such smoking results in higher than normal fetal COHb.[148,158] Gennser et al.[78] found that maternal cigarette smoking abruptly decreased the proportion of time that the fetus made breathing movements. The relation to CO is not clear. The effect of maternal smoking on surviving children is not well known. Discussion of this point is available from Longo.[148] There remain a considerable number of unanswered questions as to the influence that various levels of COHb have on the mother and on the fetus.

Impaired Groups

As pointed out in the section on cardiovascular effects, the lowest effect levels of CO (about 2.5 to 3.0 percent COHb) have been shown in subjects with cardiovascular damage. Such impairments produce low CO thresholds because there is already sufficient hypoxia of cardiac tissue to produce impairment, so that there is no reserve or compensatory capacity.

Another group that also has impaired O_2 delivery is composed of individuals with impaired cerebrovasculature. This group consists mainly of persons with obstructed vasculature due to cholesterol buildup or previous cerebrovascular injury. While on theoretical grounds it is probable that subjects with impaired cerebrovasculature would have very low thresholds for detrimental effects of CO exposure, there are no direct experimental data on the subject in either humans or laboratory animals. The possible effects of reduced O_2 supply to the CNS range from any of the behavioral effects reported to be caused by CO, to the precipitation of motor seizures or cerebrovascular accidents.

Subjects whose blood has reduced O_2-carrying capability because of either dietary or pathological anemia should also be at special risk to CO exposure. Unfortunately, the effects of CO on anemic patients or experimental animals have not been adequately studied. It can be assumed _a priori_ that anemic persons would be at greater risk than normal persons because the capacity of the O_2 transport system is reduced. Tissue oxygenation may be initially compromised due to the anemic state because mixed venous Po_2 accompanying a particular COHb value is somewhat greater in anemic than in normal subjects. In patients with hemolytic anemia and sickle cell disease,[67] the rate of endogenous CO production from heme catabolism is increased. Normal subjects produce approximately 18 moles CO/hr, resulting in COHb levels of 0.5 to 0.8 percent. Carbon monoxide production in anemic patients[46,146] has been reported to vary from 31 to 158 moles/hr, producing COHb levels of 1.3 to 5.2 percent.

Anemic individuals approach equilibrium levels of COHb more rapidly than those with normal Hb levels at any given exposure to CO. Exposure to 21.9 mg/m^3 (25 ppm) CO for approximately 4 hours in an individual with 7 g percent of Hb could result in 4 to 5 percent COHb, compared to an anticipated level of 2.5 percent for normal individuals. Exogenous CO exposure of anemic individuals, in conjunction with higher endogenous production, could result in critical levels of COHb. Subjects whose blood has low O_2-carrying capabilities due to anemia would be expected to be more sensitive to the effects of CO exposure because of the already marginal O_2 delivery system. While dietary anemias are not as great a problem as in former times, anemias resulting from various pathological conditions are still major health problems, and low levels of CO exposure could pose a health threat to such groups.

Patients with chronic obstructive pulmonary disease are probably at high risk, although few studies on them have been reported. Any increase in hypoxia could result in respiratory failure or other effects due to reduced O_2 supply. However, these individuals may absorb less CO due to their disease and may have compensated for their hypoxia by increased erythropoiesis and a shift of the O_2 dissociation curve to the right. Ogawa et al.[174] have presented evidence on the development of pulmonary edema and discussed possible mechanisms of the role of CO in the disorder. Sofoluwe[208] has described the potential further irritation of the lungs of children having bronchiolitis and bronchopneumonia by their exposure to CO derived from wood fires used for cooking purposes. Aronow et al.[11] studied 10 patients with chronic obstructive pulmonary disease who had been exposed for 1 hour to CO that raised the COHb level to 4.1 percent. When they exercised on a bicycle ergometer, dyspnea occurred within 147 seconds. However, 218 seconds elapsed before dyspnea occurred when they exercised with COHb levels at 1.48 percent. The investigators' conclusion was that their limited exercise performance was probably a cardiovascular limitation rather than a respiratory one.

Drug Users

Drugs such as alcohol, tobacco smoke, therapeutic drugs, and illicit drugs as they interact with CO exposure have been discussed under the heading of "Interactions with other pollutants and drugs." Although there is little empirical data on these interactions in either man or animals, theoretical expectations and the evidence that exists strongly indicate that individuals taking various drugs would be at special risk. The group of people under the influence of some form of drugs at any given time is so large as to include a very major part of the general population. Since interactions could be serious and the potential for them appears to be nearly ubiquitous, it is imperative that further research be done on this subject.

Unadapted Individuals

Adaptation in humans has been discussed extensively in earlier sections of this chapter and Chapter 10. The preponderance of evidence seems to indicate that people who have not adapted to high altitudes and are then exposed to both high altitude and CO simultaneously are at greater risk.

Occupational Groups

Certain occupational groups are at special risk because of the especially high exposures to CO peculiar to their work.[166] These groups include garage personnel, traffic policemen, steelworkers, firefighters, and workers in petroleum and chemical industries. The presence of chronic low-level CO poisoning may have significant influences on the health and efficiency of these workers but this awaits further study. Many other occupational exposures occur, but most studies of such exposure are complicated by the unknown or unreported smoking habits of the workers under study.[94] Table 11-6 illustrates the potential emission rates of CO for certain industries.

A study of blood COHb in the U.S. general public was carried out by Stewart and his associates,[214,215] who sampled blood drawn at blood donor mobile units in 17 urban areas and in some small towns in New Hampshire and Vermont. Kahn and his associates[57,128,228] evaluated COHb levels in metropolitan St. Louis, where a total of 45,649 donors provided blood for analysis. Stewart had 29,000 individuals (1,018 from St. Louis) and Kahn had 16,649 (all from St. Louis) in their respective samples. It should be noted that Stewart et al.'s[215] subjects were studied in March 1971 and Kahn et al.'s[128] during October 1971 to October 1972. The highest COHb values were 13.0 and 18.2 percent, respectively, in Stewart et al.'s and Kahn et al.'s samples. Tables 11-7 and 11-8 present Horvath's summary[114] of the findings of these two groups. Stewart et al.[215] concluded that 35 percent of the non-smoking donors in St. Louis were exposed to ambient CO that led to COHb levels greater than 1.5 percent, while Kahn's group[128] reported that 15.3 percent of their St. Louis non-smoking blood donors had levels above 1.5 percent. Kahn's group also stated that 21.9 percent of their donors who were non-smoking industrial workers had COHb levels of 2 percent or more, and only 5.7 percent of the remainder of the non-smoking sample had levels of 2 percent or more. Stewart et al.[217] have compared COHb levels found in subjects in Chicago in 1970 and 1974. They reported a substantial reduction in COHb levels in blood donors over this time and suggested that the reduction was caused by a decrease in ambient CO levels.

Stewart et al.[215] concluded that there were significant differences between the COHb saturations of the occupational groups studied. Students and housewives had the lowest COHb concentrations. Other low COHb groups included those associated with mental health services, education, library science, religion, art, road paving, and entertainment. The vehicle-related occupational groups had higher COHb saturations than most groups. Other high COHb groups included those associated with metal processing, chemical processing, stone and glass processing, printing, welding, electrical assembly and repair, and graphic arts. They concluded that a significant percentage of the population studied was continuously exposed to ambient CO concentrations in excess of those permitted by U.S. air quality standards.

On the other hand, Kahn and coworkers[128] concluded that ambient CO exposure was responsible for only very small increases in COHb levels in their sample. They suggested that their

TABLE 11-6. NATIONWIDE EMISSION ESTIMATES, 1977[173]
(10^6 metric tons/year)

Source Category	TSP	SO_x	NO_x	VOC	CO	Percentage of Total CO
Transportation	1.1	0.8	9.1	11.5	85.7	83.4
Highway vehicles	0.8	0.4	6.7	9.9	77.2	75.2
Non-highway vehicles	0.3	0.4	2.5	1.6	8.5	8.2
Stationary fuel combustion	4.8	22.4	13.0	1.5	1.2	1.2
Electric Utilities	3.4	17.6	7.1	0.1	0.3	0.3
Industrial	1.2	3.2	5.0	1.3	0.6	0.6
Residential, commercial, and institutional	0.2	1.6	0.9	0.1	0.3	0.3
Industrial processes	5.4	4.2	0.7	10.1	8.3	8.1
Chemicals	0.2	0.2	0.2	2.7	2.8	2.7
Petroleum refining	0.1	0.8	0.4	1.1	2.4	2.3
Metals	1.3	2.4	0	0.1	2.0	2.0
Mineral products	2.7	0.6	0.1	0.1	0	0
Oil & gas production & marketing	0	0.1	0	3.1	0	0
Industrial organic solvent use	0	0	0	2.7	0	0
Other processes	1.1	0.1	0	0.3	1.1	1.1
Solid waste	0.4	0	0.1	0.7	2.6	2.5
Miscellaneous	0.7	0	0.1	4.5	4.9	4.8
Forest wildfires	0.5	0	0.1	0.7	4.3	4.2
Agricultural burning	0.1	0	0	0.1	0.5	0.5
Coal refuse burning	0	0	0	0	0	0
Structural fires	0.1	0	0	0	0.1	0.1
Miscellaneous organic solvent use	0	0	0	3.7	0	0
TOTAL	12.4	27.4	23.1	28.3	102.7	100 100

NOTE: A zero indicates emissions of less than 50,000 metric tons.

TABLE 11-7. MEAN PERCENT OF CARBOXYHEMOGLOBIN SATURATION IN SMOKERS AND NON-SMOKERS IN ST. LOUIS[114]

	Non-smokers		Smokers	
	No. of donors	Mean	No. of donors	Mean
Kahn et al.[128]	10,157	0.85	6,492	4.58
Stewart et al.[215]	673	1.35	345	5.47

TABLE 11-8. MEAN PERCENT OF CARBOXYHEMOGLOBIN SATURATION[114]

	Non-smokers		Smokers	
	No. of donors	Mean	No. of donors	Mean
Kahn et al.[128] (St. Louis)	10,157	0.85	6,492	4.58
Stewart et al.[215] (U.S.A.)	16,036	1.43	11,289	5.21

data indicate two major sources of COHb in their subjects: smoking and work-related exposure. They stated that almost 20 percent of their sample population consisted of industrial workers who carried an added COHb burden of 1.15 percent compared with non-industrial workers. They attributed higher COHb levels not to ambient atmospheric CO but, overwhelmingly, to smoking and occupation. Most individuals with 2 or more percent COHb were industrial workers or smokers, or both. A similar conclusion was reached by others.[111,220]

Chovin[42] has provided some of the most complete information on Paris policemen, illustrating some of the concerns related to this occupational group. Similar information is provided by the studies of Balabaeva and Kalpaznov[20] on traffic policemen in four large towns in Bulgaria. Gothe et al.[89] found relatively low levels of COHb in Swedish traffic policemen.

Ramsey[185] reported a rise in COHb from 1.5 to 7.3 percent in 14 non-smoking parking garage employees exposed to an average working-day ambient CO level of 68 mg/m^3. He also noted that smokers exposed to the above environment had an initial average COHb level of 2.9 and an average COHb level of 9.3 percent at the end of the day. Non-smokers exposed to this environment had final levels of only 3.9 percent. In this regard, Ramsey stated that occupational exposure was more important than smoking. A contrary opinion was expressed by Buchwald,[36] who reported that cigarette smoking was a more significant contributor to the high levels of COHb he found in Canadian garage and service workers. Of the smokers, 70 percent had levels in excess of 5 percent, while only 30 percent of the nonsmokers had such levels. A study of employees of the Triborough Bridge and Tunnel Authority, New York City,[84] indicated that methemoglobin was slightly, although significantly increased in these workers occupationally exposed to automobile exhaust. The role of cigarette smoking was not clarified. Fristedt and Akesson[77] found a slight increase in COHb in workers employed in service installations of enclosed parking areas, but attributed the discomfort that the workers experienced to other components of automobile exhaust.

Breysse and Bovee[34] used expired air samples to determine the exposure to CO of stevedores, gasoline-powered lift-truck drivers, and winch operators. Of some 700 estimates of COHb in these workers, 5.7 percent of the workers exceeded COHb levels of 10 percent. Levels of COHb greater than 10 percent were found in 7 percent of the stevedores and 18 percent of the lift-truck operators. Smoking contributed substantially to the attainment of the high levels of COHb. Petrov[179] also studied dock workers and found COHb levels as high as 10 percent. Goldsmith's study of longshoremen[82] suggested that the alveolar concentrations of CO were age-related, regardless of smoking history. Pack-a-day smokers in the 45-to-54-year age bracket had alveolar values of 31 mg/m^3, while 75-to-84-year-olds' alveolar values were only 16 mg/m^3. Non-smokers did not exhibit this age-related pattern; even in subjects up to 84 years of age, alveolar concentrations remained at the same level.

Inspectors at U.S.-Mexico border crossing stations are exposed to ambient levels of CO that fluctuate between 6 and 195 mg/m^3.[48] Carboxyhemoglobin levels of smokers and non-smokers prior to their duty as inspectors were 4.0 and 1.4, rising to 7.6 and 3.8 percent, respectively. Johnson et al.[122] studied six fare collectors working at a highway toll booth. Ambient CO levels were 26 mg/m^3 (8-hour time-weighted average for 12 days). On 3 days, ambient CO exceeded 40 mg/m^3. Post-shift COHb ranged from 1.8 to 8.6 percent, with a high of 11.7 percent.

Non-smoking British steelworkers had end-of-shift values of 4.9 percent. Non-exposed, non-smoking controls reached 1.5 percent. Smokers had higher values, reaching levels of 7.4 percent. The highest COHb value reported was 14.9 percent.[126]

Another major source of CO is the internal combustion engine, which may in some cases be considered an occupational source since it provides many forms of transportation. Community CO levels in ambient air follow a regular diurnal pattern of variation, however, and different concentrations have been measured at different sites. Jech and Ubl[120] measured alveolar concentrations of CO in individuals during a 2-hour stay on a busy street and reported a considerable increase in expired CO levels during that period. Likewise, the passenger compartment of vehicles provides a potentially hazardous occupational area. Carbon monoxide may enter this compartment from faulty or damaged exhaust systems or from the air surrounding roadway traffic. Carbon monoxide levels in the compartment may be higher than those found outside the vehicle. Haagen-Smit[98] found average concentrations in a vehicular passenger compartment to be 42 mg/m^3 on a Los Angeles freeway during rush hour traffic (higher concentrations up to 80 mg/m^3 have been reported recently). It has been reported that concentrations in excess of 115 mg/m^3 occur in some vehicle interiors.

Direct measurement of COHb in firefighters engaged in fighting fires of extremely long duration indicated that 10 percent of these individuals had COHb values in excess of 10 percent.[85] Sammons and Coleman[200] reported that firefighters had changes in those enzymes related to myocardial damage and that these changes were related to their COHb levels. However, the high levels of COHb in the control (non-firefighters) and test (firefighters) groups make these conclusions somewhat suspect.

Besides contributing to exposure of employees to CO, industry also contributes to the pollution of the surrounding atmosphere. Gas generator plants,[170] smelters,[163] steelworks,[37,126,152] plastic works,[3] electric power generating plants,[91] and mines[169] have all been suggested as sources of environmental CO pollution. Workers in a cast iron foundry were also found to have high COHb levels associated with various CNS and cardiovascular disorders.[63] Hernberg et al.[109] evaluated 1000 foundry workers who were exposed to CO, heat, and strenuous physical work. The presence of angina pectoris showed a clear dose-response relation with regard to CO exposure from either occupation or smoking, or both.

Rural work establishments, especially those involving intensified livestock production facilities, can produce high ambient levels of CO. Carbon monoxide concentrations up to 229 mg/m^3 have been found in these facilities, with both the animals and workers having high levels of COHb.[165] Recreational facilities may also be problem areas. Excessive levels of CO were found in ice-skating arenas where ice-resurfacing machines were used. Levels as high as 348 mg/m^3 (400 ppm) CO were found in such an arena after complaints of illness in children skating there were reported to the local health department.[125] Johnson et al.[124] reported on eight school children who became sick from CO while in a school bus. Subsequent testing for ambient CO concentrations in school buses showed that 36 percent of bus interiors tested had levels of CO in excess of EPA standards for an 8-hour exposure. Improperly regulated space heaters in enclosed areas can also produce high concentrations of CO. Bondi et al.[30] reported that, on a submarine patrol of 40 days, the COHb levels of subjects were 2.1 and 1.7 percent at the beginning and end of the patrol, respectively.

The belated discovery that at least one chemical substance utilized in industry and commerce is degraded within the body to CO has potentially significant epidemiological and clinical implications. Halogenated hydrocarbons have been widely utilized as organic solvents, replacing carbon tetrachloride. A chance observation[211] indicated that the inhalation of one of these, dichloromethane (methylene dichloride, CH_2Cl_2), was followed by a sustained elevation of COHb concentration. Inhalation of 500 to 1000 ppm of CH_2Cl_2 (Industrial Threshold Limit Value is 500 ppm) for 1 or 2 hours resulted in COHb levels exceeding 14 percent.[212] This elevation of COHb continued beyond the time of exposure and gradually returned to normal during the next 24-hours. Fodor and Roscovanu[73] exposed human volunteers to 500 ppm CH_2Cl_2. After 8 hours of exposure, COHb levels were approximately 12 percent. Exposure to 100 ppm resulted in raising COHb levels to 5 percent. Elimination of CO was slow, so that 24 to 26 hours were required to reestablish the control COHb levels. Residual alterations in pulmonary function were still noted 3 months later.

Several investigators have studied the influence of CH_2Cl_2 on physiological function. Astrand et al.[13] examined the effects of CH_2Cl_2 on work performance. Central nervous system depression was observed in some subjects.[212] Winneke[233] compared the effects of exposure to ambient CO (up to 115 mg/m^3) and CH_2Cl_2 on vigilance performance. Although he noted no effects related to CO, he found a striking decrement in vigilance consequent to CH_2Cl_2 exposure. A potentially more dangerous complication of CH_2Cl_2 exposure has been indicated by Stewart and Hake:[216]

> ". . . because it is so sustained following exposure, the cardiovascular stress produced by elevated COHb levels, derived from CH_2Cl_2 metabolism, is greater than that resulting from equally high COHb levels derived from CO."

They report on an individual who experienced three episodes of myocardial infarction, each following the use of a paint remover. About 80 percent of CH_2Cl_2 is metabolized to CO;[60,72,137,161,188,195] the mechanism remains to be elucidated. Roth et al.[195] have noted that animals rarely succumb to CH_2Cl_2 (11,520 ppm), possibly because of saturation of the pathways by CH_2Cl_2 metabolism and/or rates of CO excretion.

The possible detrimental health effects of chemical compounds that may be metabolized to CO deserve further investigation.

SUMMARY

From the foregoing review of the literature pertaining to effects of low-level CO exposures on humans and experimental animals, it may be concluded that CO deleteriously affects mainly the cardiovascular and central nervous systems. While many data are ambiguous, poorly documented, and often in dispute, it still seems safe to conclude that cardiovascular effects can be demonstrated with CO exposures as low as 17 to 21 mg/m^3 CO (15 to 18 ppm CO for an 8-hour exposure; 2.5 to 3.0 percent COHb). For behavioral and CNS effects, a minimum of 29 to 34 mg/m^3 CO (25 to 30 ppm CO; 4 to 6 percent COHb) seems to be required. Visual sensitivity might be affected as a continuous dose-response function without an obvious CO threshold, but such data are presently tenuous.

There are important data to be acquired before an appraisal can be made of the general health effects of CO. Fragments of data seem to point to the importance of CO and its interactions with other pollutants with which it commonly occurs. Far too little information exists regarding the effects of exposures to CO in combination with other pollutants, as opposed to the effects of CO by itself.

There are suggestions that CO might interact with drugs in a significant way. Apparently fetuses, health-impaired individuals, individuals under the influence of drugs, and persons not previously adapted to high altitudes or CO exposures are at special risk, but the nature of the risk, much less its magnitude, cannot even be estimated from the present literature.

It appears that acute CO exposures to 17 to 21 mg/m^3 (15 to 18 ppm) may be adverse to human health. This range of values represents the level at which the first detectable effect occurs in persons with cardiac impairment. The question of the significance of this and other findings is a matter of general dose-response functions. While only preliminary information is available on this subject, as discussed above, the findings in the present literature may be summarized (see Table 11-9). These data are of little use, however, if drugs and other pollutants alter the responses of individuals who have multiple impairments. It represents a minimum known set of effects that could under some circumstances be much worse or that could occur at lower thresholds. Further data are urgently needed.

TABLE 11-9. ESTIMATED HEALTH EFFECTS LEVELS FOR CARBON MONOXIDE EXPOSURE*

Effects	COHb concentration, %	Approximate Ambient CO levels to produce stated COHb, mg/m^3 in resting individuals		Reference
		1-hour	8-hour	
Physiologic norm	0.30-0.7	0	0	Coburn, et al., 1969[45]
Passive smoking** aggravates angina pectoris	1.8-2.3	(29-70 ppm)	(6-15 ppm)	Aronow, 1978[12]
Decreased excercise capacity in patients with angina pectoris, intermittent claudication, or peripheral arteriosclerosis	2.5-3.0	79-97 (70-85 ppm)	17-21 (15-18 ppm)	Aronow and Rokaw, 1971[5] Anderson et al., 1973[2] Aronow and Isbell, 1973[7] Aronow et al., 1974[8]
Impairment of vigilance tasks in healthy experimental subjects	3.0-6.5	97-239 (85-207 ppm)	21-52 (18-45 ppm)	Horvath et al., 1971[113] Groll-Knapp et al., 1972[92] Fodor et al., 1972[71]
Increased angina*** attacks for freeway travel				Aronow et al., 1972[6]
Impairment of myocardial** function in patients with coronary heart disease				Aronow et al., 1974[9]
Decreased exercise performance in normal persons				Aronow and Cassidy, 1975[10]
Decreased exercise performance in patients with chronic obstructive pulmonary disease				Aronow et al., 1977[11]

TABLE 11-9 (continued)

Effects	COHb concentration, %	Approximate Ambient CO levels to produce stated COHb, mg/m^3 in resting individuals		Reference
Linear relationship between COHb and decreasing maximal oxygen consumption during strenuous exercise in young healthy men	5-20	176-887 (155-175 ppm)	38-193 (33-170 ppm)	Ekblom et al., 1972[64] Horvath, et al., 1975[115] *Ayres et al.[18;19]
Statistically significant diminution of visual perception, manual dexterity or ability to learn				Bender et al., 1971[25]

* - High variability in COHb levels is found between individuals exposed to similar CO levels.
** - Partial effects may be due to other pollutants found in cigarette smoke.
*** - Partial effects may be due to other pollutants found in automotive exhaust and the ambient air.

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APPENDIX A: GLOSSARY

Abscissa: The horizontal or x axis of a graph.

Abscission: The process of cutting off, as in the dropping of leaves.

Absorbance: The ability of a layer of a substance to absorb light or other radiation, expressed mathematically as the negative logarithm of the fraction of light intensity transmitted.

Absorptivity: The absorbance of a solution of unit concentration in a layer of unit thickness.

Adiabatic: A process occurring without loss or gain of heat.

Adrenaline: British name for epinephrine, a potent stimulator of the autonomic nervous system.

Adsorption: The adhesion of molecules in an extremely thin layer to the surfaces of solids or liquids with which they are in contact.

Alveolar: Pertaining to the alveoli or small air pockets of the lungs.

Alveolar-arterial pressure difference ($A\text{-}aD_{O2}$): Difference in oxygen pressure between the lung alveoli and the arterial blood.

Ambient air: The surrounding, well-mixed air.

Aminotransferase: Any of a class of enzymes that catalyzes the transfer of an amino group from one molecule to another, typically from an alpha-amino acid to an alpha-keto acid.

d-Amphetamine: A central nervous system stimulant.

Anaerobic: Living, or active, in the absence of free oxygen.

Anemia: A reduction below normal in the number of erythrocytes (red blood cells) per cubic millimeter, in the quantity of hemoglobin, or in the volume of packed red cells per 100 milliliters of blood.

Angina pectoris: A paroxysmal thoracic pain, with a feeling of suffocation and impending death, due usually to anoxia of the heart muscle, and precipitated by effort or excitement.

Angiogram: An X-ray picture of a blood vessel filled with a contrast medium.

Angstrom: A unit of wavelength of light, equal to one ten-billionth of a meter, or 10^{-8} cm.

Anoxia: Absence or lack of oxygen; reduction of oxygen in body tissues below physiologic levels.

Anthropogenic: Relating to the impact of man and his activities on the natural world.

Aortic intima: Innermost lining of the aorta (main trunk from which the body arteries proceed).

Arteriosclerotic heart disease (ASHD): Sclerosis and thickening of the walls of small arteries (arterioles) of the heart.

Asanguineous: Bloodless; the blood is replaced by another fluid.

Atheroma: A mass of plaque of degenerated, thickened arterial lining occurring in atherosclerosis.

Atheromatosis: The process involving fatty degeneration of the inner coat of an artery.

Autonomic nervous system: The portion of the nervous system concerned with regulation of the activity of the heart muscle, the smooth muscle, and the glands; self-regulatory.

Autotrophic: Needing only carbon dioxide or carbonates as a source of carbon, and a simple inorganic nitrogen compound for metabolic synthesis.

Auxin: Plant "hormone" that promotes growth in plant cells and tissues.

Bacteroids: Enlarged, branched bacteria found in the nodules of leguminous plants.

Ballistocardiogram (BCG): Tracing from the apparatus for recording the movements of the body due to the heartbeat.

Biosphere: The part of the world in which life can exist.

C_3 type plant: A type of plant in which the first stable product of photosynthesis is a compound containing three carbon atoms, namely phosphoglyceric acid.

Cannabis sativa: Hemp; contains cannabinol, an hallucinogenic; variously called bhang, ganja, hashish, or marihuana.

Carboxyhemoglobin (COHb): The compound formed by the combination of carbon monoxide with hemoglobin.

Carboxymyoglobin (COMb): The compound formed by the combination of carbon monoxide with myoglobin.

Carcinogenesis: The development of a carcinoma, a malignant new growth of epithelial cells.

Cardiac index: The rate of blood pumping by the heart, divided by the surface area of the body; expressed in units of liters per minute per square meter.

Cardiovascular: Pertaining to heart and blood vessels.

Catecholamine: One of a group of compounds having a sympathomimetic action such as norephinephrine, epinephrine, and dopamine.

Catheter: a tubular, flexible surgical instrument for withdrawing fluids from, or introducing fluids into, a cavity of the body.

Central nervous system (CNS): Brain and spinal cord together.

Cerebral blood flow (CBF): Blood flow through the cerebrum or main portion of the brain.

Cerebral cortex: Outer layer of the brain.

Cerebrovascular: Refers to blood vessels of the brain.

Chemical kinetics: The study of the rate or speed at which one chemical substance is converted into another.

Chemiluminescence: Light emitted during a chemical reaction.

Chemoreceptor: Specialized cells adapted for excitation by chemical substances, such as found in the senses of smell and of taste.

Chronaxie: The minimum time an electric current must flow at a voltage twice the minimal potential necessary for stimulation for the muscle to contract.

Claudication: Limping or lameness; a complex of symptoms frequently associated with occlusive arterial diseases of the limbs.

Colorimetric: A type of chemical analysis in which the amount of a chemical substance present is found by measuring the light absorption due to its intrinsic color or the color of another substance into which it can be completely converted.

Contingent negative variation (CNV): Slow-wave brain potentials evoked by a stimulus.

Coronary: Pertaining to the arteries and veins of the heart.

Coulometric: A type of chemical analysis in which the amount of a substance present is determined by causing it to undergo an electrochemical reaction and measuring the amount of electricity needed to carry the reaction to completion.

Critical flicker fusion frequency (CFFF): The frequency at which intermittent flashes of light appear as a steady or continuous light.

Cynomolgus: Monkeys of the genus Macaca, particularly the species M. irus, used in laboratory research.

Cytochrome: Iron-containing respiratory pigment for intracellular oxidation.

Cytochrome oxidase: A blood protein enzyme found in cells, usually attached to mitochondria (rod-shaped organelles), associated with copper.

Debye: A unit of electric moment equal to 10^{-18} stat coulomb-centimeter; a measure of the electrical asymmetry of a molecule.

Diastole: The dilatation of the heart, filling the ventricles with blood.

Differential-reinforcement-of-low-rate schedule: A reinforcement schedule in operant conditioning that requires the subject to respond at a specified, relatively low rate to be rewarded.

Diffusion: The process by which particles of gases, liquids, or solids intermingle as a result of their spontaneous movement caused by thermal agitation, and move from a region of higher concentration to a region of lower concentration.

Diurnal: Having a daily cycle.

Dyspnea: Difficulty of breathing; labored breathing.

Echocardiogram (ECG): A tracing made by an echocardiograph, which records the position and movement of the heart wall or internal structures by analysis of the echoes obtained from ultrasonic waves directed through the chest.

Electrocardiogram (EKG): A tracing made by an electrocardiograph, which measures changes of electrical potential occurring during the heartbeat.

Elution: The release or removal of a substance by a solvent, from a material which had retained the substance for a time.

Endogenous: Originating within the organism.

Epicotyl: The upper portion of an plant embryo or seedling.

Epidemiology: The study of the relationships of the various factors determining the frequency and distribution of diseases in a human community.

Epinasty: The downward curling or curving of a foliage leaf.

Equivalent Method: A method of sampling and analyzing air for a pollutant that has been officially designated as an equivalent method by the Environmental Protection Agency. It must have a consistent relationship to a reference method when both methods are used to measure the concentration of the pollutant in a real atmosphere.

Ergometer: An apparatus measuring the work performed by a group of muscles.

Erythrocyte: Red blood cell (corpuscle).

Erythropoiesis: The formation of erythrocytes (red blood cells).

Erythropoietin: Substances regulating the production of red blood cells.

Ethanol: Ethyl alcohol.

Etiolation: Paleness due to the exclusion of light.

Etiology: Pertaining to the factors that cause disease and the method of their introduction to the host; the sum of knowledge regarding causes.

Exogenous: Originating from outside the organism.

Exothermic reaction: A chemical transformation in which heat or other energy is liberated.

Fibrillation (cardiac): Rapid, irregular contractions of the muscle fibers of the heart.

Fixed-constant-number schedule: A reinforcement schedule in operant conditioning that requires the subject to emit a specific number of responses before reinforcement (food) is available; early approaches to the food tray reset the response requirement.

Fixed interval schedule: A reinforcement schedule in operant conditioning that requires that a specified time interval elapse before a response is reinforced.

Fixed ratio schedule: A reinforcement schedule in operant conditioning that requires a specified ratio of responses to reinforcements.

Fourier transform spectroscopy: An improved method for obtaining absorption spectra of high quality. All of the available radiant energy is sent continuously through the sample (in contrast to conventional instruments in which only a very narrow band of wavelengths is used at any moment, the remainder being discarded) and the absorption spectrum is reconstructed by optical and mathematical processing.

Gas chromatography: A method of chemical analysis in which a mixture of gases or vapors is separated into its components by passage (in an inert carrier gas) through a column of material which interacts more or less strongly with the individual components, retaining them for longer or shorter times before release into the effluent gas stream.

Gaussian distribution: Synonymous with normal distribution.

Globin: The protein constituent of hemoglobin.

Glycolysis: The breakdown of glycogen or glucose into lactic acid.

Haldane constant: Ratio of the stability constant for carboxyhemoglobin to that for oxyhemoglobin; a measure of the relative affinity of hemoglobin for carbon monoxide as compared to its affinity for oxygen.

Half-time: The time required for the concentration, or amount, of a substance to decrease to half its initial value.

Hectare: A metric measure of area containing 10,000 square meters (2.471 acres).

Hematocrit: The volume percentage of erythrocytes (red blood cells) in whole blood.

Hemoglobin (Hb): Iron-containing protein respiratory pigments occurring in the red blood cells of vertebrates and transporting oxygen to the tissues and carbon dioxide from the tissues.

Hemopoiesis: Hematopoiesis, the formation and development of blood cells.

Hexobarbital: A sedative and an hypnotic.

Histopathology: Pertaining to diseased tissues of the body.

Hopcalite: A catalyst for converting carbon monoxide to carbon dioxide, which consists of a mixture of oxides of copper, cobalt, manganese, and silver.

Hydrocyanic acid (HCN): An aqueous solution of hydrogen cyanide; a poisonous liquid used chiefly in fumigating and in organic syntheses.

Hydroxyl radical: Unstable, electrically neutral fragment of a molecule containing one oxygen atom and one hydrogen atom. It is formed by disruption of a water (or other hydroxyl-containing) molecule, as a result of exposure to far ultraviolet light or other high-energy radiation such as X-rays.

Hyperpnea: Abnormal increase in the depth and rate of the respiratory movements; heavy or labored breathing.

Hypertrophy: The enlargement or overgrowth of an organ or part due to an increase in size of its constituent cells.

Hypobaric hypoxia: Deficiency of oxygen due to less than normal pressure.

Hyponasty: The upward curling or curving of a foliage leaf.

Hypothalamus: Part of the brain; has many functions, e.g., regulation of water balance, body temperature, sleep, food intake, and development of secondary sex characteristics.

Hypothermia: Abnormally low temperature.

Hypoxemia: Deficient oxygenation of the blood; hypoxia.

Hypoxia: Low oxygen content or tension. Anemic hypoxia is due to reduction of the oxygen-carrying capacity of the blood as a result of a decrease in the total hemoglobin or an alteration of the hemoglobin constituents.

Hypoxic hypoxia: A term used to denote hypoxia due to low oxygen tension to distinguish it from that due to carboxyhemoglobin in which CO replaces O_2.

Intercalated disks: Short lines or V-shaped stripes extending across the fibers of heart muscle.

Intraperitoneal: Within the body cavity.

In vitro: Outside the living organism.

In vivo: Within the living organism.

Ischemia: Deficiency of blood: myocardial ischemia, deficiency of blood supply to the heart muscle.

Isopleth: On a map, a line connecting points at which a particular variable has a specified constant value.

Lactate dehydrogenase (LDH): An enzyme that catalyzes the dehydrogenation of alpha hydroxy acids to alpha keto acids; in certain cases, specifically restricted to lactate.

Leghemoglobin: A pigment found in leguminous root nodules.

Leucine aminopeptidase: A proteolytic enzyme that catalyzes the hydrolysis of peptide linkage involving the amino acid, leucine.

Lipids: Various substances including fats, waxes, phosphatides, cerebrosides and related or derived compounds.

Lognormal: A type of statistical distribution in which the logarithm of a variable has a normal distribution, in contrast to the familiar case in which the variable itself has a normal distribution.

Methylene chloride (Dichloromethane; CH_2Cl_2): A compound which causes an elevation of carboxyhemoglobin; a commercial solvent.

Microflora: Microscopic plant life; bacteria.

Microglial: Pertaining to the microglia, small non-neural, interstitial cells that form part of the supporting structure of the central nervous system.

Microwave rotational spectroscopy: A method for chemical analysis of gases by measuring the absorption of electromagnetic radiation in the centimeter wavelength region, which is based on the characteristic rotational frequency of the specific gas molecule.

Milligrams per cubic meter (mg/m^3): A measure of concentration of a substance. In this instance, the weight in milligrams of CO contained in one cubic meter of the ambient air, which may be converted to "parts per million" at one atmosphere by multiplication by the factor 0.873 at $25^\circ C$, or by the factor 0.800 at $0^\circ C$. At pressures other than one atmosphere (760 torr) such a factor should be multiplied by an additional factor of 760/p, where p is the ambient pressure in torr.

Mitochondria: Small organelles found in the cytoplasm of the cell and which are concerned with cellular metabolism.

Mixing ratio: The ratio of the mass of a substance (such as water vapor) in an air sample, to the total mass of all the other substances in the same air sample.

Mole: Gram molecular weight. The amount of a substance represented by writing "grams" after its molecular weight (the sum of the atomic weights of all the elements in its formula). One mole of any substance contains 6.02×10^{23} molecules.

Mossbauer spectroscopy: A method for chemical analysis and structure studies, based on small variations (due to chemical and physical factors) in the energy of gamma rays emitted by radioactive atoms.

Multiple schedule: A reinforcement schedule in operant conditioning in which two or more component schedules operate in alternation, each in the presence of a different stimulus.

Myelin: A lipid substance forming a sheath around some nerves.

Myocardial infarction: A necrotic (dead) area of the heart muscle.

Myocardium: Muscle of the heart.

Myocardosis: Disorder of the middle, thick muscle layer of the heart wall.

Myoglobin: A protein found in muscle fibers, which is similar to hemoglobin in its reversible binding of oxygen.

Necrosis: Localized death of living tissue.

Neonate: A new-born infant.

Normal distribution: A type of statistical distribution in which the set of values obtained in a large number of independent repetitions of a measurement can be represented by a symmetrical bell-shaped curve.

Nuclear magnetic resonance: A type of radiofrequency spectroscopy used for chemical analysis and molecular probes, based on small changes (caused by nearby electrons) in the magnetic energy levels shown by certain atomic nuclei.

Orsat: An apparatus or method for chemical analysis of gas mixtures, in which each gas successively is removed from the sample by an appropriate chemical reagent, and the decrease in volume or pressure is measured after each step.

Oxygen partial pressure (Po_2): The amount of pressure exerted by oxygen as one component of a mixture of gases, equal to the pressure it would exert if it were alone in the same container. The total pressure of a gas mixture is the sum of the partial pressures of the individual gases.

Oxyhemoglobin: The compound formed by the combination of oxygen with hemoglobin.

Oxymyoglobin: The compound formed by the combination of oxygen with myoglobin.

Paradigm: An example or pattern.

Parts per million (ppm): A measure of concentration of a substance. In this instance, the volume in liters of CO contained in 1,000,000 liters of the ambient air, which may be converted to "milligrams per cubic meter" by multiplication by the factor 1.145 at 25°C, or by the factor 1.250 at 0°C. At pressures other than one atmosphere (760 torr) such a factor should be multiplied by an additional factor of p/760, where p is the ambient pressure in torr.

Pathology: Study of the structural and functional changes produced by diseases, e.g., abnormalities.

Photic: Pertaining to light.

Photochemistry: Study of the effects of light, ultraviolet rays, or other radiant energy in causing conversion of one chemical substance into another.

Photolysis: Disruption of a molecule caused by exposure to ultraviolet or other radiation energy.

Photometry: Measurement of light intensity; can be used for chemical analysis by measuring the intensity change caused by characteristic absorption or emission of radiant energy due to a chemical compound.

Planck's Radiation Law ($hv = E$): Planck's constant (h) times the frequency of radiated energy (v) equals quanta of energy (E).

Plume: An elongated mobile column, as of smoke or exhaust gases.

Porphyrin: Iron-free pyrrole derivatives which form the basis for respiratory pigments.

Postpartum: Following parturition or giving birth to offspring.

Primordia (flower): Earliest stage in the development of the flower.

Progressive ratio schedule: A reinforcement schedule in operant conditioning that requires the subject to emit a progressively increasing number of responses (within limits) to obtain each successive reinforcement.

Protoporphyrin: An iron-free derivative of hematin, $C_{34}H_{35}N_4FeO_5$, which together with globin forms hemoglobin.

Psychomotor: Pertaining to motor effects of cerebral or psychic activity.

Psychotropic: Exerting an effect upon the mind; usually applied to drugs that affect the mental state.

Pyrrole: A liquid, weakly basic, cyclic substance (C_4H_4NH) obtained in the destructive distillation of various animal substances.

Radicals: Unstable fragments of molecules which have an unpaired electron and tend to react or change rapidly into more stable substances.

Rapid eye movement (REM): An indication that the sleeping subject has entered one of several "stages" characteristic of normal sleep.

Reference method: The method of sampling and chemical analysis for a pollutant substance which has been officially designated as acceptable by the Environmental Protection Agency; includes a specific instrument which must be used in such analysis.

Scavenger: A chemical substance which removes radicals by a rapid reaction, converting them to more stable substances.

Second derivative spectrometer: An instrument for detecting weak absorption peaks by electronic processing of spectral intensity measurements, to yield the rate of change of the slope of the absorption spectrum plotted as a function of wavelength. This makes the peaks much more visible.

Sequela (ae): A lesion or affection following or caused by an attack of disease.

Sickle-cell anemia: A disease marked by anemia and by ulcers and characterized by the red blood cells of the patient acquiring a sickle-like or crescentic shape *in vitro*; the disease is apparently confined to the negro race and it is hereditary.

Sigmoid: Shaped like the letter S.

Sink: An absorber of a substance, or a process which acts as a removal or dissipation mechanism.

Soret: Intense peaks of light absorption shown by hemoglobin and related compounds, in the spectral region of about 400 to 440 nanometers; named for the discoverer.

Spectrophotometer: An instrument for measuring the relative light intensities (or absorption of light) at different wavelengths in a spectrum; used for chemical analysis of substances which have characteristic colors or absorption spectra.

Stoichiometric: The amount of a chemical substance theoretically needed to react with, or produced by a reaction from, a specified amount of another substance, as expressed quantitatively by the chemical equation for the reaction.

Stratosphere: An upper region of the earth's atmosphere, above about 10 to 16 kilometers, in which clouds are rare and there is little change of temperature with altitude.

ST segment: The segment of the electrocardiogram between the f-wave and the t-wave. The electrocardiogram is characterized by four waves, arbitrarily called Q, R, S, and T.

Superior colliculus: A portion of the brain primarily concerned with visual responses.

Synergism: The joint action of agents so that their combined effect is greater than the algebraic sum of their individual effects.

Systole: Contraction of the heart, forcing the blood out through the arteries.

Teratology: Science that deals with abnormal development of the fetus, and congenital malformations.

Terpene: A type of hydrocarbon found in plant oils, resins, and balsams, such as those produced by pine or other conifers.

Torr: A unit of pressure equal to 1/760 of an atmosphere, roughly equal to one millimeter of mercury in the Torricelli barometer, or 1333 dynes per square centimeter.

Tropopause: The region of the earth's atmosphere which marks the transition from the troposphere below to the stratosphere above, at an altitude of about 10 to 16 kilometers, depending on latitude, season, and weather.

Troposphere: The portion of the earth's atmosphere which extends from the surface out to an altitude of about 7 to 10 miles or 10 to 16 kilometers.

Valence electrons: The electrons in the outmost shell of the atom which determine the extent to which an atom may combine with other atoms.

Vascular: Of or pertaining to the blood vessels.

Vasodilation: Dilation of a blood vessel, increasing the blood flow.

Ventilation perfusion ratio (V_A/Q): A measure of the rate of O_2 exchange between lung alveoli and arteries.

Vigilance: A stage of alertness requiring continuous attention over long periods of time.

Virtual source: A point from which divergent beams seem to emanate but do not actually do so.

Visual evoked response (VER): Reaction to a visual stimulus.

White noise: A heterogeneous mixture of sound waves extending over a wide frequency range.

Zoxazolamine: Skeletal muscle relaxant; promotes excretion of uric acid in the urine.

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